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Organoboron Reagents and Recent Strategies in Rhodium Catalysed Additions

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Organoboron reagents and recent strategies in rhodium catalysed additions

Volume 1 of 1

Hannah Joy Edwards

A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department of Chemistry

September 2011

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[*H. J. Edwards*]

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Abstract

The research presented herein is concerned with the exploration of the rhodium catalysed addition of organoboron reagents.

Chapter 1 firstly introduces the area of organoboron reagents, focussing on the applications of potassium alkenyl trifluoroborate reagents. Secondly, an extensive discussion of the rhodium catalysed conjugate addition of organoboron reagents demonstrates its utility as a key coupling step in recent syntheses.

Chapter 2 describes synthetic methods towards alkenylboron reagents and describes the synthesis of functionalised and enantiopure alkenyl trifluoroborate salts.

Chapter 3 discusses the rhodium catalysed addition of potassium alkenyl trifluoroborate salts to α,β -unsaturated compounds. A gas chromatography study addresses issues concerning protodeboronation and highlights the potential for olefin transposition. A new rhodium catalysed olefin transposition reaction has been thoroughly investigated and applied using the synthesised potassium alkenyl trifluoroborate salts.

Chapter 4 describes the synthesis of biologically relevant, enantiopure dihydropyranones for use as acceptors in the rhodium catalysed conjugate addition reaction. The hetero-Diels-Alder reaction is employed to synthesise the dihydropyranones. Rhodium catalysed conjugate addition of arylboronic acids and potassium alkenyl trifluoroborates is utilised to concisely assemble late stage intermediates of natural products including diospongin B.

Chapter 5 describes the synthesis and characterisation of the compounds discussed in chapters 2, 3 and 4.

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Abbreviations

α,β -O	α,β -olefin
β,γ -O	β,γ -olefin
γ,δ -O	γ,δ -olefin
Ac	acetyl
Acc	acceptor; amide, ester, ketone
aq	aqueous
Ar	aryl
9-BBN	9-borabicyclo(3.3.1)nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Bod	bicyclo[3.3.1]nona-2,6-diene
^t Bu	tertiary butyl
°C	degrees Celsius
CA	conjugate addition
calcd	calculated
Cod	1,5-cyclooctadiene
δ	chemical shift in parts per million downfield from trimethylsilane
d	day(s); doublet (spectral)
DAN	1,8-diaminonaphthalene
DIFLUORPHOS	5,5'-bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole
DOLEFIN	5-benzyl-8-methoxy-1,8-dimethyl-2-(2'-methylpropyl)-bicyclo[2.2.2]octa-2,5-diene
d ⁱ ppf	1,1'-bis(diisopropylphosphino)ferrocene
dpp	3,5-diphenylphenyl
Dppf	1,1'-bis(diphenylphosphino)ferrocene
d ^t Bupp	1,1'-bis(ditertbutylphosphino)ferrocene
DMF	dimethylformamide
eq.	equivalent(s)
Fc	ferrocene
H ₈ -Binol	2,2'-dihydroxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl
HC	heck-type coupling
HD	heck-type diene
Hz	hertz
IBX	2-iodoxybenzoic acid
IR	infrared
<i>J</i>	coupling constant (in NMR spectroscopy)
KIPBH	potassium triisopropoxyborohydride
m-CPBA	meta-chloroperbenzoic acid
MIDA	<i>N</i> -methyliminodiacetic acid
m	multiplet
Mp	melting point
MPBH	methylpentanediolborane
MVK	methyl vinyl ketone
<i>m/z</i>	mass-to-charge ratio (in mass spectrometry)
nbd	Norbornadiene
NMO	<i>N</i> -methylmorpholine- <i>N</i> -Oxide
NMR	nuclear magnetic resonance
Ph	Phenyl
ppm	parts per million

Pr	propyl
q	quartet (spectral)
R _f	retention factor (chromatography)
Rt	room temperature
s	singlet
t	triplet
TBA	tetra- ⁿ butylammonium
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TBS	<i>tert</i> -butyldimethylsilyl
tfb	tetrafluorobenzobarrelene
TFP	tri-2-furylphosphine
TPAP	tetrapropylammonium perruthenate
t _R	retention time

Chapter 1: Organoboron reagents and their synthetic applications in rhodium catalysed conjugate addition reactions.

Aim: A review of organoboron reagents as reactive and versatile organometallics, in particular a discussion of the synthesis and applications of alkenyl trifluoroborates. An overview of the rhodium catalysed conjugate addition of organoboron reagents and its utility as a key coupling step in recent syntheses.

1.1 Introduction

Carbon-carbon bond formation is one of the most desirable transformations across synthetic chemistry; a transformation facilitated by the use of organometallic reagents (R-M). As such, organometallic reagents are an important class of compounds widely utilised across synthetic chemistry disciplines to gain access to organic materials.¹

Organomagnesium and organolithium compounds have been widely utilised, however their high nucleophilicity and basicity renders them incompatible with sensitive functionality and they are highly sensitive to air and moisture. Therefore, for a number of decades, chemists have been searching for more selective and functional group tolerant organometallics, which gave rise to cuprates, organozincs, silicates, aluminates, organoborons, and stannanes.²

Of all those available, organoboron compounds have become widely popularised and have distinct advantages including: low toxicity, stability to air and moisture and easy accessibility both synthetically and commercially.

Traditionally, boronic acids have been the most widely studied and employed in the largest range of applications. They are used throughout organic synthesis in a variety of reactions, predominantly C-C and C-N formations, as biologically active pharmaceutical agents and sensors.³ As the application of organoboron reagents throughout organic synthesis has increasingly diversified⁴, so too have the reagents. Organoboron compounds have expanded from boronic acids and boronic esters to trifluoroborates, boroxines, boronate esters, tetra aryl boronates, and triolborates; each created in order to improve its synthetic utility.

Alkenyl organoboron compounds more recently emerged as valuable coupling reagents. They allow for the inclusion of more varied functionality which is particularly useful for natural product and drug synthesis owing to the prevalence of alkyl groups.

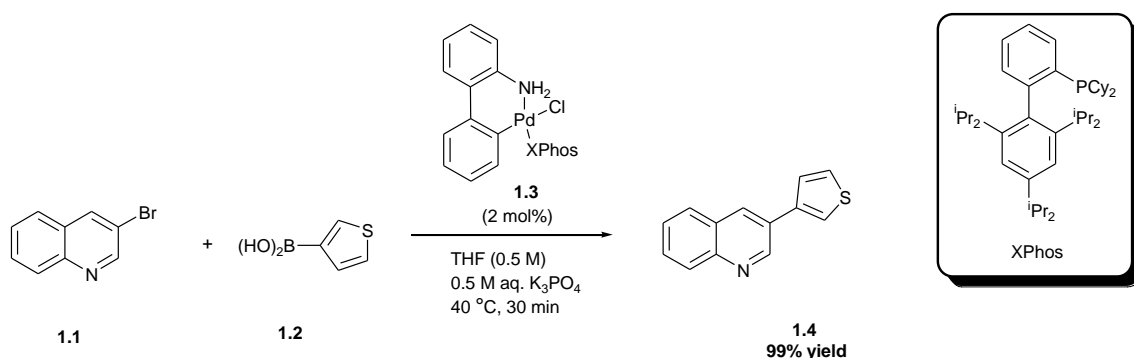
Organoboron reagents feature predominantly in transition metal catalysed reactions, most commonly in Suzuki-Miyaura reactions.⁵ Another key utilisation of organoboronates and the focus of our work has been in the rhodium catalysed 1,4-addition of organoboronates to α,β -unsaturated systems.

1.2 Organoboron reagents as organometallics

1.2.1 Boronic acids

Since 1860⁶ boronic acids have become increasingly popular with a variety of applications.⁷ They have been found to exhibit a range of biological activity when present in a number of natural products,^{8,9,10} potentially therapeutic compounds¹¹ and as sugar sensors.¹² However, their main application remains as synthetic reagents. Over 450 boronic acids are commercially available and their stability and easy preparation has made them versatile reagents in a variety of reactions. The most significant application is in the Suzuki-Miyaura reaction¹³; a palladium catalysed cross-coupling reaction of aryl boronic acids.

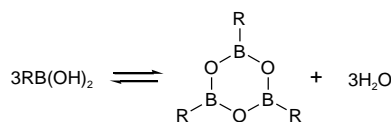
It is common practise to employ an excess of boronic acid in reactions, predominately owing to their tendency to protodeboronate. Alkenyl and heteroaryl boronic acids as well as some aryl boronic acids are highly desirable, yet very challenging cross coupling partners, often deboronating under elevated temperatures which renders them redundant in such reactions. A recent publication has overcome the synthetic limitations of protodeboronation and demonstrated successful Suzuki-Miyaura reactions with particularly challenging aryl and heteroaryl boronic acids, (Scheme 1.1).¹⁴



Scheme 1.1

The key for this reaction's success was the new pre-catalyst **1.3**. This rapidly forms the active Pd(0) species under mild conditions which reduced the rate of deboronation.

Some boronic acids, are waxy solids which can be difficult to purify and isolate. In particular alkenylboronic acids are readily polymerised and as such are difficult to isolate.¹⁵ A further complication is the equilibrium formation of trimeric cyclic anhydrides or boroxines (Scheme 1.2).¹⁶

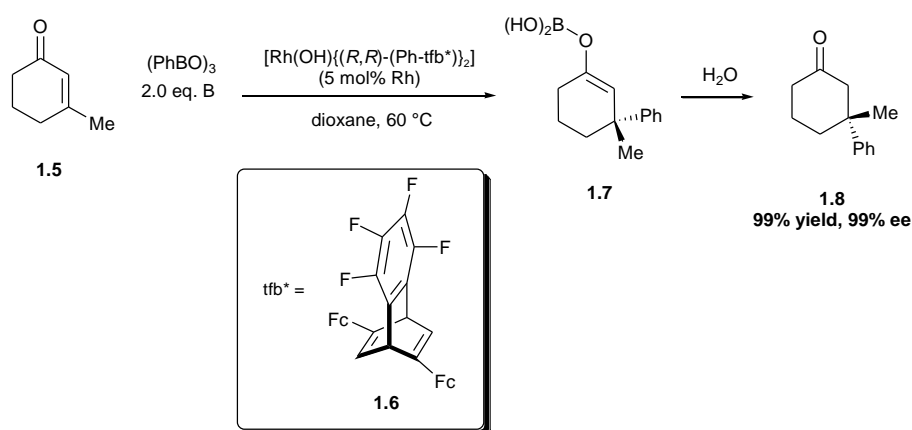


Scheme 1.2

Although this does not directly affect the coupling process, it is difficult to distinguish the amount of boronic acid versus boroxine and therefore reaction stoichiometry can be affected. To improve reactivity and overcome limitations such as protodeboronation, stability and isolation, alternative protecting groups have emerged.

1.2.2 Boroxines

Recently, boroxines have been formed purposefully and employed as reagents in rhodium catalysed conjugate addition reactions. They have been used with particularly challenging substrates, β,β -disubstituted α,β -unsaturated ketones, which are employed in constructing all carbon quaternary centres.¹⁷ An asymmetric conjugate addition of phenylboroxine to ketone **1.5** is achieved in excellent yield and enantioselectivity using an enantiopure chiral tetrafluorobenzobarrelene (tfb*) ligand **1.6**, (Scheme 1.3). These tfb* ligands produce isolatable hydroxorhodium complexes with high catalytic activity.



Scheme 1.3

1.2.3 Boronic esters

Boronic esters are very common and solve many of the boronic acid's problems. Pinacol esters (**1.9**) are stable to column chromatography and as such are easier to isolate and are monomeric species. However, the expense and overall waste of the necessary diols is not atom efficient or economical. Catechol and alkyl-9-borabicyclo[3.1.1] (9-BBN) are also useful protecting groups, but the organoboron reagents **1.10** and **1.11** are air sensitive and more difficult to purify (Figure 1.1). They are usually synthesised *via* transesterification with the desired diol or boronation with the desired boronate.

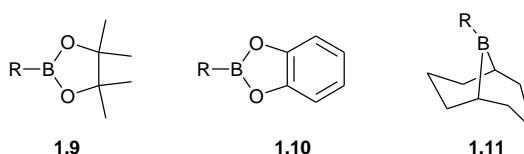


Figure 1.1

1.2.4 Benzoxaboroles

Benzoxaboroles are internally stabilised esters that, similarly to boronic acids, exist as dimers (Figure 1.2). However, unlike boronic acids they cannot form larger lattices (ie trimers etc.) as only one hydroxyl group is present at the boron.¹⁸

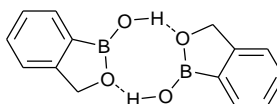
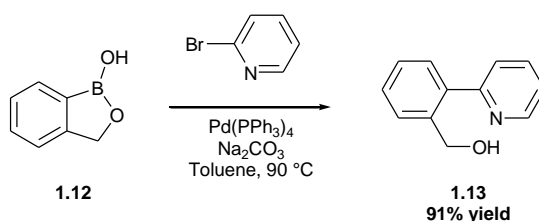


Figure 1.2

Compared to the corresponding *o*-hydroxymethylphenylboronic acids, they are more stable, less prone to boron-carbon hydrolytic cleavage and more soluble in water.¹⁹ The ring B-O bond is also very stable compared to other boronic esters.²⁰ Therefore the synthesis of benzoxaboroles requires either boronation of a benzyl alcohol or introduction of a hydroxymethyl to the corresponding boronic acid.¹⁸ They have also shown promising biological activity including antifungal,²¹ anti-inflammatory and antibacterial.²²

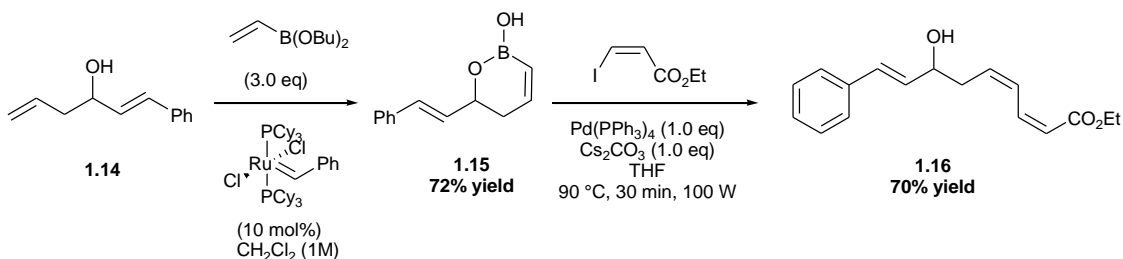
Their reactivity is similar to that of boronic acids such that benzoxaboroles have been successfully utilised in a number of synthetic reactions including the palladium catalysed Suzuki reaction (Scheme 1.4).²³



Scheme 1.4

1.2.5 Alkenyl boronic half acids (oxaborinenes)

Similarly to benzoxaboroles, internal stabilisation of the boronic acid is also possible for alkenyl boronic acids and takes the form of alkenyl half boronic acids. In a recent example mono substituted cyclic alkenyl boronic half acids have been synthesised using metathesis and applied in Suzuki reactions as shown in Scheme 1.5.²⁴ The *cis* geometry of the double bond is exclusively generated in the oxaborinene species **1.15** and is neatly retained through the Suzuki reaction to generate *cis*-olefins.



Scheme 1.5

1.2.6 Organoboronates

A major drawback of organoboron compounds, in particular alkenyl and heteroaryl boronic acids, has been their instability. Compared to most aryl boronic acids, alkenyl, alkyl, alkynyl, and heteroaryl organoboranes are more unstable under atmospheric conditions and rapidly decompose under standard reaction conditions. This instability is owing to the vacant orbital on boron which can be attacked by oxygen or water resulting in decomposition of the reagent.²⁵ Common decomposition pathways include protodeboronation,²⁶ oxidation and polymerisation.¹⁵ It has been a synthetic challenge to improve organoboron reagent stabilities and overcome the undesired side reactions.

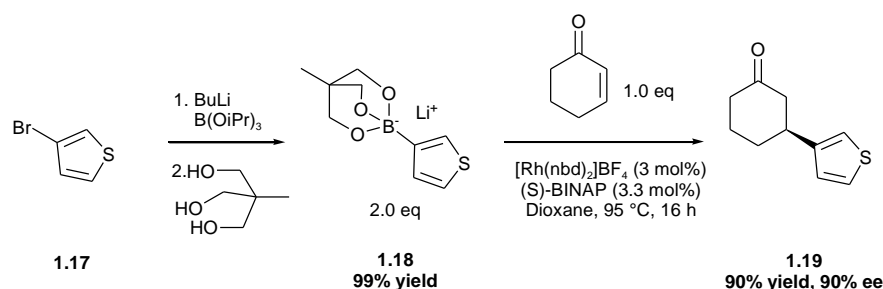
In recent years, quaternisation of the boron atom with an anionic ligand has formed tetracoordinate ‘ate’ complexes which have become key compounds for application in

metal-catalysed reactions. The high air and water stability of these ‘ate’ complexes makes alkenyl and heteroaryl boronates stable and easily accessible reactive reagents.

1.2.7 Triolborates

Cyclic triol borates (**1.18**) are exceptionally stable in air and water. Both, lithium and potassium triolborates successfully transmetalate to complete palladium²⁷ catalysed C-C and copper catalysed C-N couplings.²⁸ One of the major advantages of triol borates over other organoboronic acids and esters is their high solubility in organic solvents which allows anhydrous reactions and prevents carbon-boron hydrolytic cleavage.

The triolborates’ reactivity and stability has facilitated the application of previously unusable heteroarylboron reagents in rhodium catalysed conjugate additions. Scheme 1.16 shows the successful addition of thiophene triolborate **1.18** to cyclohexenone in excellent yield and enantioselectivity.²⁹



Scheme 1.16

1.2.8 Aminoboron reagents

In the search for crystalline, air-stable, monomeric and chromatographable organoboron reagents came the discovery of MIDA boronates **1.20** by Burke and co-workers^{30,31,32} and the DAN protecting group **1.21** by Suginome and co-workers (Figure 1.3).^{33, 34, 35} The benefit of these masked boronic acids is in orthogonal cross coupling.

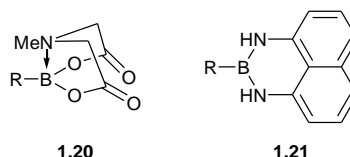
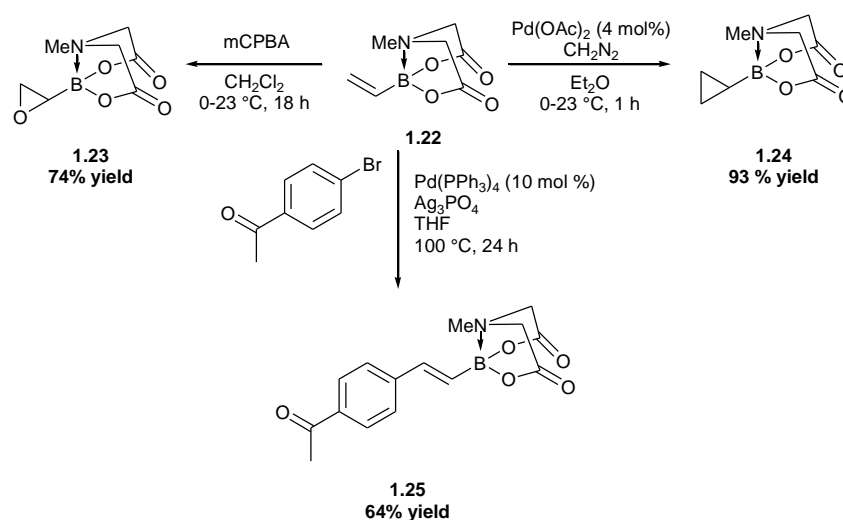


Figure 1.3

Similarly to triol borates, the MIDA protecting group has shown utility in making 2-heterocyclic boronates stable and accessible.³⁶ MIDA, whilst facilitating the synthesis, handling and storage of air stable boronates, has the added advantage of being a relatively cheap, commercially available and environmentally friendly protecting group.³⁷ Nitrogen complexation to the boron reduces Lewis acidity by changing it from a sp^2 to a sp^3 centre which accounts for the decrease in reactivity of these reagents.

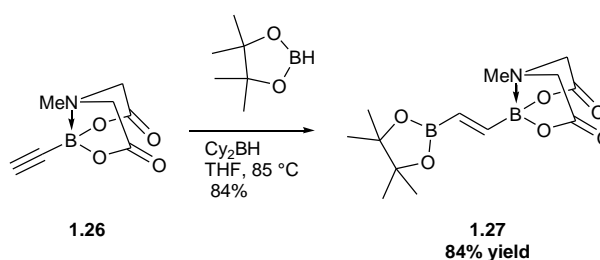
MIDA boronates are typically synthesised by Dean-Stark esterification with MIDA. Under anhydrous conditions, the MIDA boronate is inert to cross coupling reactions, but can readily be hydrolysed to the boronic acid under mild aqueous base.^{30,32} Therefore, these stable protected boronates allow further derivatisation of the molecule while maintaining the carbon-boron bond. MIDA boronates have been shown to tolerate a huge number of reaction conditions including Jones oxidation, allowing early incorporation of boron, and further functionalisation.³¹ Vinyl MIDA boronate **1.22** has been further functionalised to give access to a number of MIDA boronates (Scheme 1.7).³⁸ The stability of MIDA boronates against protodeboronation also allows access to challenging examples such as cyclopropyl and oxiranyl boranes, **1.24** and **1.23** respectively.



Scheme 1.7

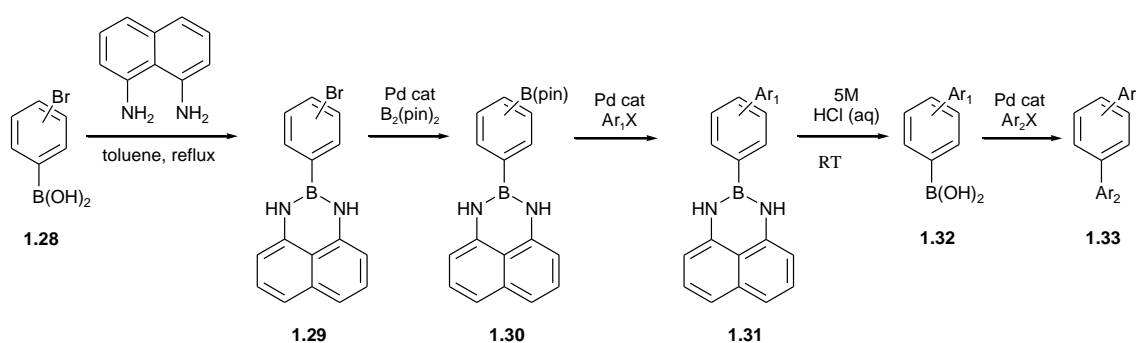
More recently, ethynyl MIDA boronate **1.26** has been hydroborated to generate orthogonally protected alkenyl diboron species **1.27** as shown in Scheme 1.8.³⁹ This could be employed in an iterative, orthogonal cross coupling process, first with the pinacolalkenylboronate under anhydrous conditions, then under aqueous base conditions, slow release of the alkenyl boronic acid could complete a further coupling.

The slow *in situ* release has made previously poor boronic acids employable as MIDA boronates.



Scheme 1.8

Whilst the DAN protecting group has similar reactive properties to the MIDA protecting group, it is not a boronate. The DAN group masks the boron centre from reactivity by decreasing its Lewis acidity through π -electron donation from the nitrogen atoms. Their preparation is similar to that of MIDA boronates *via* azeotropic removal of water and their strategy in synthesis is also for differentially protected diorganoboron reagents such as **1.30**.⁴⁰ Suginome's boron masking strategy is outlined in Scheme 1.9. The DAN group is unreactive towards cross coupling conditions, so the reactive boronic ester can be coupled to form **1.31**. Subsequent deprotection of the DAN group under acidic conditions unmasks free boronic acid **1.32** which can be employed in a second cross coupling.

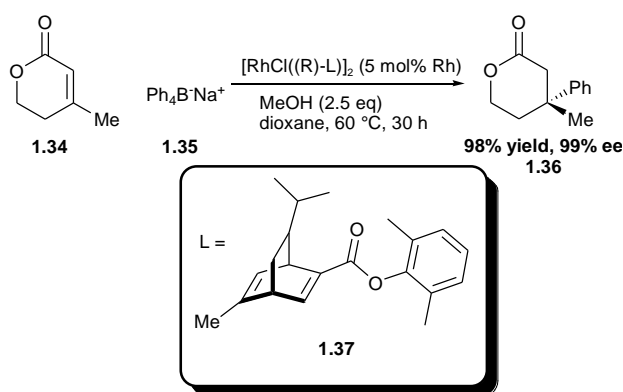


Scheme 1.9

Despite a number of significant and highly desirable advantageous features, a significant drawback of both MIDA and DAN protecting groups is that their own cross coupling ability mimics that of boronic acids. They either require deprotection prior to use or provide a slow release of boronic acid in the reaction. Significant drawbacks of these reagents are increased synthetic steps, atom inefficiency, and a large excess of the boronate is still required in cross coupling reactions.⁴¹

1.2.9 Tetraarylborates

In recent years, tetraarylborates have emerged as air stable, effective nucleophiles for challenging metal catalysed reactions. In particular in reactions where other organoboron nucleophiles have been unsuccessful, such as rhodium enantiopure diene catalysed 1,2-addition to imines^{42,43} and 1,4-addition to β,β -disubstituted α,β -unsaturated ketones.⁴⁴ They have also been shown to undergo rhodium catalysed conjugate addition in high yield and enantioselectivity to the more challenging, less reactive β,β -disubstituted α,β -unsaturated esters such as **1.34**, by employing chiral diene ligand **1.37** (Scheme 1.10).⁴⁵



Scheme 1.10

1.2.10 Potassium and *tert*-butylammonium trifluoroborate salts

Potassium organotrifluoroborates first emerged in 1960⁴⁶ as boronate complexes, but their utility was not fully recognised until much later.⁴⁷ These protected organoboronates are monomeric, crystalline and indefinitely stable to air and moisture. They can be stored indefinitely at room temperature, but are also highly reactive in a large variety of reactions; a highly desirable combination.^{48,49,50}

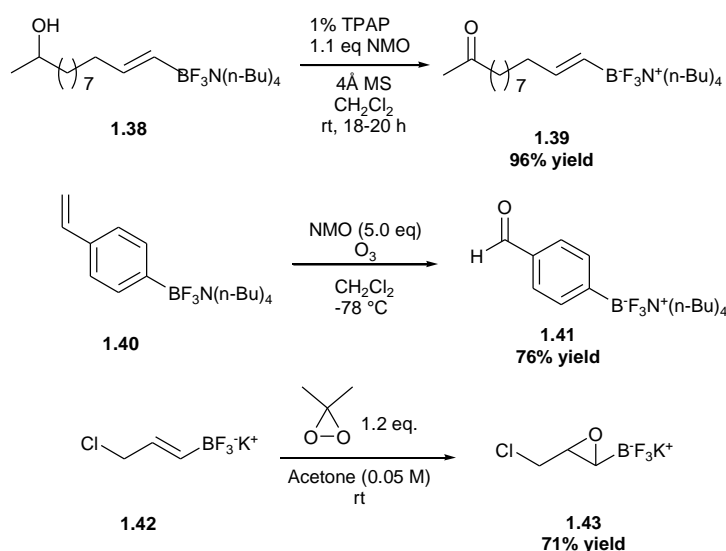
The stability of organotrifluoroborates is owing to the tetra-coordinate nature of the boron combined with the strength of the boron-fluorine bonds. This has proved particularly valuable for the protection of unstable boronic acids. For example, alkenyl boronic acids are highly useful coupling partners, but are particularly unstable as the vacant orbital on boron can be attacked by oxygen or water resulting in decomposition.²⁵ Formation of the trifluoroborate prevents this mechanism from occurring, making alkenylboronates bench stable, accessible reagents.

Since their introduction, other counter ions have been used to improve specific properties. The most useful alternative is the *tetra*-*n*-butylammonium (TBA) counter ion

which increases solubility in chlorinated solvents such as dichloromethane.⁵¹ Lithium and magnesium trifluoroborates are less stable; decomposition occurs owing to the fluorophilic nature of the counter ions. The caesium counter ion has also been reported,⁵² however, potassium and sodium form the most stable trifluoroborates.⁵³

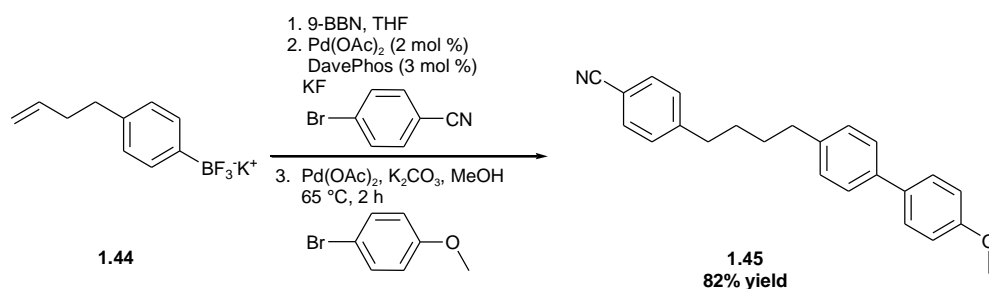
The robust nature of trifluoroborate salts allows remote functional group manipulation whilst maintaining the carbon-boron bond. As the first organoboron protecting group to enable this there has been much research in this area, mainly by Molander and co-workers. Carbon-boron bond stability towards other reactions has been superseded in recent years by new MIDA and DAN protecting groups, which are also stable to silica chromatography. However, potassium trifluoroborate salts remain cheaper, more easily synthesisable and more reactive reagents in coupling reactions; they possess similar protective properties without the need for a separate deprotection step.

The most impressive examples of trifluoroborate carbon-boron stability are towards oxidative conditions, which are typically incompatible with most organoboron compounds. Both potassium and TBA trifluoroborate salts tolerate many common oxidation protocols including Swern, Dess-Martin, TPAP/NMO, TEMPO, IBX and ozonolysis (Scheme 1.11).⁵⁴ The ability to incorporate a carbonyl moiety into an organoboron is especially useful as aldehydes and ketones are incompatible with many hydroboration methodologies.⁵⁵ Also, epoxidation of alkenyl trifluoroborates with dimethyldioxirane is not only successful, but also generates extraordinarily stable epoxytrifluoroborates such as **1.43**.⁵⁶



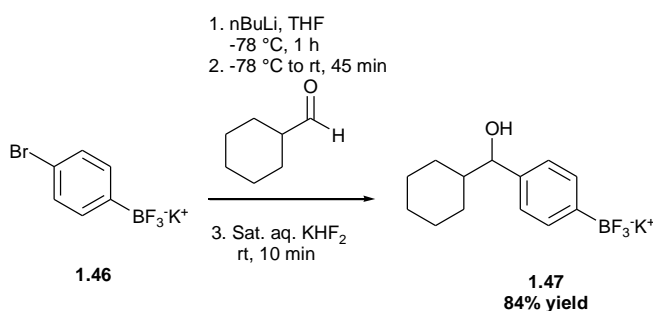
Scheme 1.11

As with MIDA and DAN organoborons, trifluoroborate salts can also be used in orthogonal diboron compounds for bi-directional cross coupling reactions. The reactivity of trifluoroborate salts in transition metal catalysed reactions can be controlled by tuning the reaction conditions. For example, hydroboration of alkenyl containing trifluoroborate salts, using 9-BBN, generates a trialkylborane which can undergo a selective cross coupling to produce further functionalised trifluoroborate salts. These can then undergo a second cross coupling, by tuning the reaction conditions to form compound **1.45** (Scheme 1.12).⁵⁷



Scheme 1.12

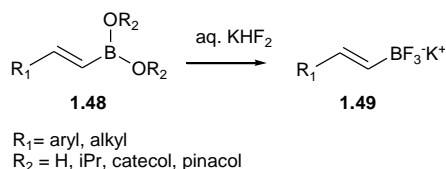
Normally, borane and boronate esters act as Lewis acids towards Grignard and alkyllithiums. However, another excellent feature of trifluoroborate salts is their ability to remain inert to lithium-halogen exchange for further functionalisation. For example, *para*-bromo substituted phenyltrifluoroborate salt **1.46** was reacted with butyllithium and quenched with benzaldehyde to afford trifluoroborate salt **1.47** (Scheme 1.13).⁵⁸



Scheme 1.13

1.2.11 Synthesis of trifluoroborates and their interconversion with other organoborons

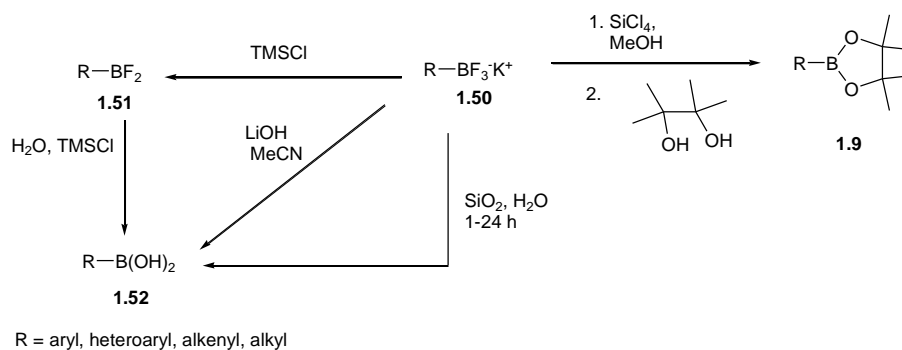
Potassium trifluoroborates can be readily interconverted between other organoboron compounds cheaply and conveniently. In general, potassium trifluoroborates are synthesised by fluorination of boronic acids, boroxines⁴⁹ and esters⁵⁹ using inexpensive potassium hydrogen difluoride (Scheme 1.14). The protocol reported by Vedejs in 1995⁶⁰ and modified by Genêt⁴⁷ has now become standard procedure.



Scheme 1.14

As this methodology is so efficient, it has been used as a way of deprotecting boronic esters, including alkyl pinane and pinacol diols to more easily removable fluoroborane intermediates.⁶¹

A number of fluorophiles have been used to deprotect trifluoroborates and allow their conversion into other organoboron compounds (Scheme 1.15). Yuen reported the effectiveness of various alkali metal hydroxides and carbonates in aqueous acetonitrile or acetone at deprotecting trifluoroborates to boronic acids.⁵⁹ Vedejs has also demonstrated deprotection of trifluoroborates *via* the difluoroborane **1.51** using anhydrous TMSCl.⁵³



Scheme 1.15

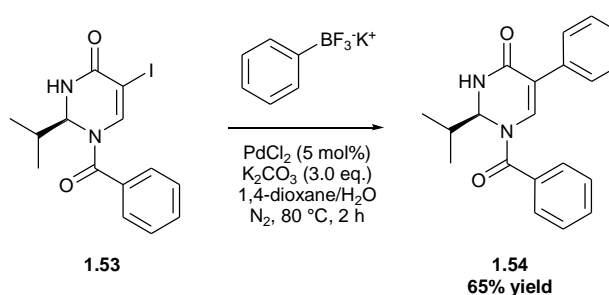
More recently, Molander has demonstrated a mild and general method for trifluoroborate hydrolysis to boronic acids using aqueous silica gel.⁶² It is interesting to note that at higher temperatures (50 °C) protodeboronation was observed.

Matteson and co-workers have reported transforming trifluoroborate salts into boronate esters **1.9** via the dichloroborane intermediate by treating with SiCl₄ in methanol followed by pinacol.⁶³

1.2.12 Applications of trifluoroborate salts

Genêt and co-workers were the first to report successful cross coupling of potassium trifluoroborates.⁶⁴ Since then, they have been widely applied in a number of transition metal catalysed reactions.⁶⁵ They are replacing other organoboron species, especially boronic acids, owing to their favourable properties and reactivity. Their most widely known application is in the Suzuki-Miyaura reaction where they have shown improvements over boronic acids and boronate esters which are hampered by competing homocoupling and protodeboronation, and also alkenylboronates which tend to be unstable.¹⁶ The cross coupling of aryl and alkenyl trifluoroborate salts has been demonstrated with an array of electrophilic partners, including aryl and heteroaryl triflates,⁶⁶ aryl tosylates,⁶⁷ heteroaromatic^{68,69} and aryl halides^{70,71} and alkenyl bromides.⁷²

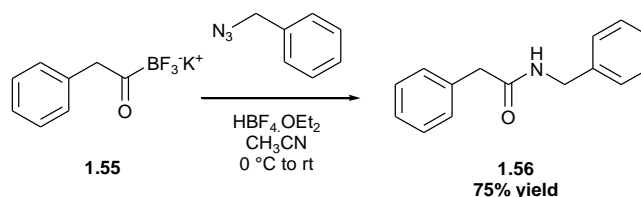
A recent publication where aryl and alkynyl potassium trifluoroborates have replaced boronic acids and esters in the Suzuki reaction, is in the arylation and alkynylation of α -iodoenones.⁷³ The developed conditions tolerate a wide range of substituted potassium trifluoroborate salts and α -iodoenones. For example in Scheme 1.16, potassium phenyl trifluoroborate successfully cross couples with α -iodoenone **1.53**.



Scheme 1.16

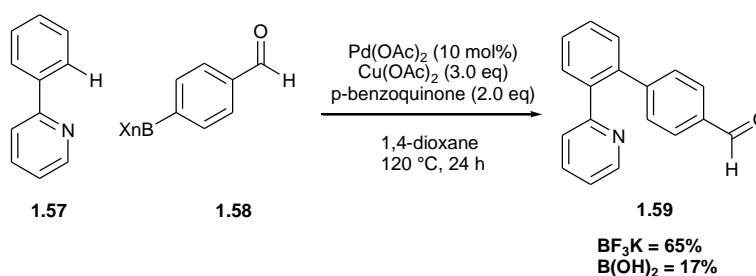
Dihaloboranes have been shown by Matteson and co-workers to react with azides to form secondary amines. As Lewis-acid activated trifluoroborates are precursors to difluoroboranes, Molander and co-workers have since synthesised an acyl trifluoroborate and reacted it with alkyl azides to form amides.⁷⁴ Only acyl potassium

trifluoroborate (**1.55**) was synthesisable *via* their method and it only coupled to alkyl azides (Scheme 1.17).



Scheme 1.17

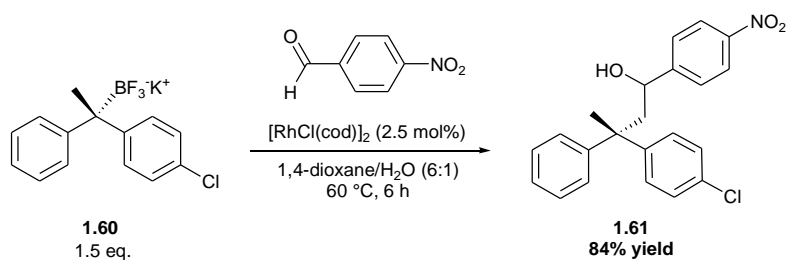
Boronic acids have previously been employed in palladium catalysed C-H bond activations. However, these reagents very often undergo undesired competing homocoupling in the reaction resulting in low to modest yields of the desired product. Considering the advantages of potassium trifluoroborate salts over boronic acids it is no surprise they complete *ortho*-arylation of 2-phenylpyridines more efficiently than the corresponding boronic acids (Scheme 1.18).⁷⁵



Scheme 1.18

Rhodium catalysed 1,2-additions of organoborons to aldehydes has also been expanded by the replacement of boronic acids and esters with potassium trifluoroborates. Aryl and alkenyl trifluoroborates have been employed successfully^{76,77} and more recently alkyltrifluoroborates have been utilised by Aggarwal and Ros.⁷⁸

The increased rate of transmetallation for potassium trifluoroborates is a particular advantage for alkyl boron derivatives, which normally have a slow rate of transmetallation and rapidly undergo β -hydride elimination. However, it would appear the mechanism for the reaction may not involve transmetallation, but simply rhodium coordination to both the boronate and aldehyde. Impressively, secondary and tertiary enantiopure trifluoroborates, such as **1.60**, have been reacted with aldehydes with complete retention of stereochemistry and in good yield (Scheme 1.19).



Scheme 1.19

Trifluoroborates are generally reported as non toxic, but similarly to boronic acids they are being discovered to have medicinal applications. The first biological investigation by Srebnik and co-workers reported potassium trifluoroborates as non covalent, non competitive and reversible serine protease inhibitors. Boronic acids are known protease inhibitors, but trifluoroborates were more active and their activity is attributed to fluorine hydrogen bonds within the active site.⁷⁹ There has been a recent study into the toxicology and antinociceptive properties of potassium thiophene-3-trifluoroborate.⁸⁰ Infact, orally administered thiophene potassium trifluoroborate induced only minor toxicity, while reducing peritoneovisceral pain induced by acetic acid without altering locomotor activity. Such findings present a great potential for trifluoroborates along side their current use in synthetic organic chemistry.

1.2.13 Alkenyl trifluoroborate salts

Alkenylboron reagents offer functionality more applicable to natural product synthesis with the ability to introduce alkenyl chains. They offer extension of existing methodology used by aryl organoboron reagents.

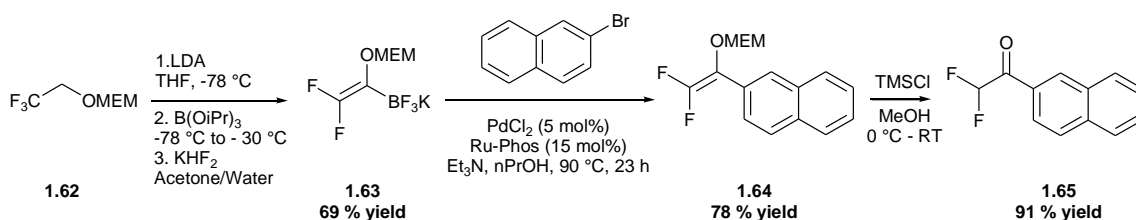
The potassium trifluoroborate protecting group is of particular benefit to alkenyl boronates, which otherwise tend to be highly unstable and difficult to purify. Alkenyl trifluoroborates on the other hand are easily accessible, highly stable yet reactive organoboron reagents.

1.2.14 Applications of potassium alkenyl trifluoroborate salts

Since their introduction as useful reagents and as their synthesis has become easier, there has been an explosion of applications of potassium alkenyl trifluoroborate salts. In 2002 Molander demonstrated the scope of potassium alkenyl trifluoroborate salts in the

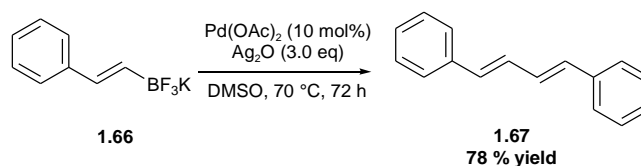
Suzuki-Miyaura reaction.⁸¹ This remains their most utilised application and over the years there have been numerous publications improving conditions, using microwaves,⁸² aqueous media⁸³ and expanding the scope of cross coupling partners to more difficult aryl⁸⁴ and allyl⁸⁵ chlorides and vinyl tellurides.⁸⁶

A recent, noteworthy application is the synthesis of *gem*-difluoroketones.⁸⁷ These are valuable compounds for medicinal chemistry and accessing them using trifluoroborate salts is far more preferable than stannanes used in previous methods. 1-alkoxyalkenylboronates are of themselves unusual and the required trifluoroborate enol ether **1.63** is accessed *via* classical borylation methodology (Scheme 1.20). In the Suzuki reaction with aryl halides these trifluoroborate salts were far superior to boronic acids and esters, proving easier to handle and less prone to decomposition so only 1.1 eq. was required for full conversion. Typical Suzuki conditions PdCl₂(dppf)CH₂Cl₂ with NEt₃ gave a decent 70% yield with arylbromides. However, switching the ligand to Ru-phos increased the yield to 91% and also enabled cross coupling with arylchlorides and iodides in 78% and 48% yield respectively. The conditions tolerate highly *ortho*-substituted aryl bromides, as well as electron withdrawing and electron donating substituents. Finally, simple MEM deprotection of the aryl enol ether **1.64** with TMS chloride generates the desired *gem*-difluoroketone **1.65** (Scheme 1.20).



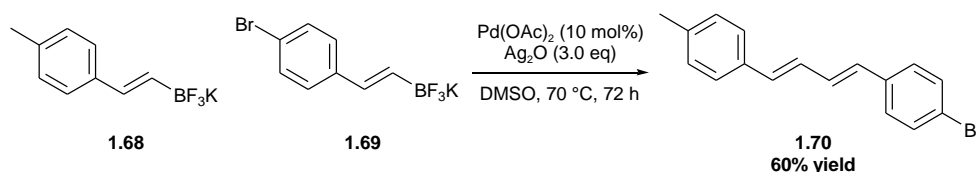
Scheme 1.20

Homocoupling is sometimes an unwanted by-product in cross-coupling reactions, but has been optimised for potassium alkenyl trifluoroborates to synthesise symmetrical 1,3-dienes such as **1.67** as shown in Scheme 1.21. A range of potassium alkenyl trifluoroborate salts self coupled using Pd(OAc)₂ and Ag₂O as a co-oxidant. Aromatic potassium alkenyl trifluoroborates gave higher yields than aliphatic potassium alkenyl trifluoroborates and (*E,E*)-dienes were observed in all cases.⁸⁸



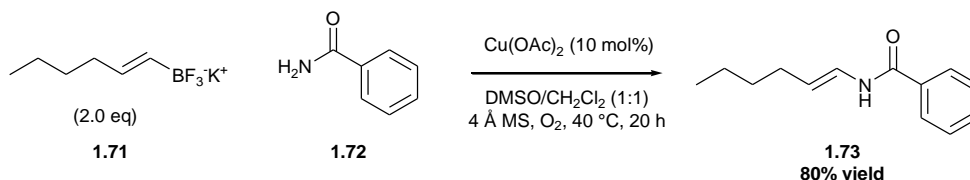
Scheme 1.21

Weber and co-workers also reported that by using two different potassium alkenyl trifluoroborate salts, cross coupling occurs in preference to homocoupling (Scheme 1.22). This is the first example of cross-dimerisation of potassium alkenyl trifluoroborate salts to synthesise unsymmetrical 1,3-dienes.



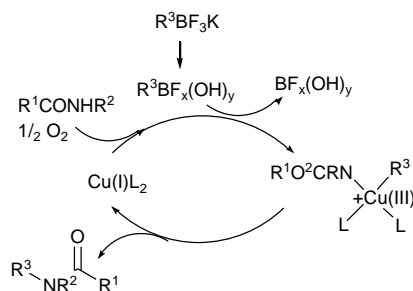
Scheme 1.22

Building on the work of Lam and co-workers on C-N formations,⁸⁹ alkenyl trifluoroborates have been cross coupled with amides to form enamides such as **1.73**, as shown in Scheme 1.23. Under mild oxidative conditions, 10 mol% $\text{Cu}(\text{OAc})_2$ and 4 Å molecular sieves, coupling is successful with a variety of amides, imides, carbamates, benzamides and acetamides, with retention of alkene configuration.⁹⁰ For high pKa amides such as oxazolidinone, pyrrolidinone and benzamide, no ligand was required, but a 1:1 CH_2Cl_2 :DMSO solvent system was necessary to aid solubility. However, for low pKa amides including phthalimide, istatin and hydroxypyridine, dichloromethane is sufficient for solubility, but 20 mol% N-methylimidazole is required. The need for ligand N-methylimidazole with more acidic amides may be to stabilise a higher oxidation state of copper, or to act as a base to deprotonate the amides and facilitate their coordination to copper. Whatever its role, with less acidic amides it has a detrimental effect on the reaction, possibly competing with their binding to copper.



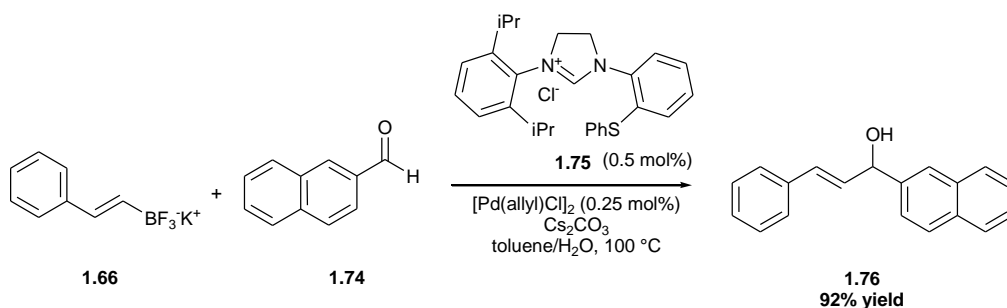
Scheme 1.23

While the precise catalytic cycle remains unknown, a general mechanism has been hypothesised as outlined in Scheme 1.24. It involves stepwise oxidation of Cu(I) to Cu(III), transmetalation of the organoboron species to either Cu(II) or Cu(III), followed by rapid reductive elimination to regenerate Cu(II) and eliminate the enamide.



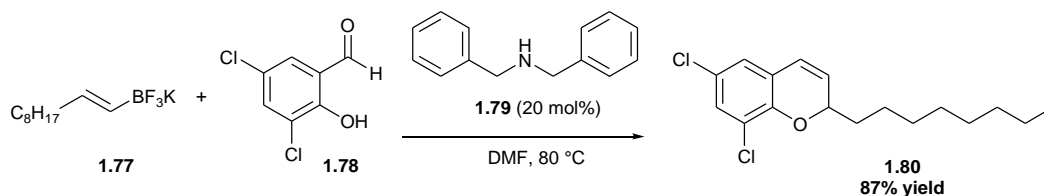
Scheme 1.24

Organoboronic acids have long been employed in the rhodium catalysed 1,2-addition to aldehydes, but it was not until more recently that alkenyl and aryl trifluoroborates have been applied. Over time, other catalytic systems have also been utilised. Shirai and co-workers have demonstrated palladium catalysed 1,2-addition using thioether-imidazolium carbene ligand **1.75** (Scheme 1.25).⁹¹



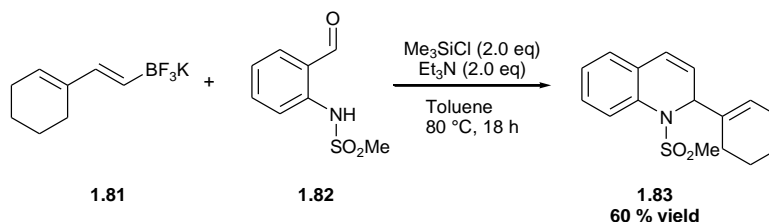
Scheme 1.25

Similar 1,2-additions have also been completed by the Petasis reaction. Different amines have been used as catalysts for the synthesis of potentially biologically relevant products. For example, potential new TGF- β inhibitor **1.80** has been synthesised by reacting 2*H*-chromene **1.78** and alkenyl trifluoroborate **1.77** in the presence of dibenzylamine (Scheme 1.26).⁹²



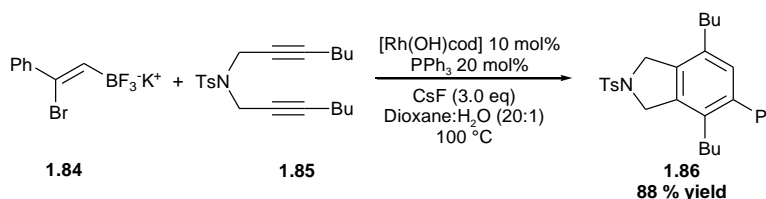
Scheme 1.26

Recently the addition of potassium alkenyl trifluoroborate salts to salicylaldehydes has been completed by Petasis and Butkevich to synthesise chromenes and dihydroquinolines. This amine catalysed 3-component Mannich type reaction is an extension of the Petasis reaction.⁹³



Scheme 1.27

A new application of potassium alkenyl trifluoroborate salts has been in the rhodium catalysed [2+2+2] cycloaddition with 1,6-diynes as a practical synthesis of poly substituted benzene derivatives (Scheme 1.28).⁹⁴ It utilises (Z)-2-bromoalkenyl trifluoroborates such as **1.84** and nitrogen, oxygen or carbon linked diynes such as **1.85**.



Scheme 1.28

A major application of alkenyl trifluoroborate salts is in the rhodium catalysed conjugate addition reaction with α,β -unsaturated carbonyl compounds. These will be discussed in detail later.

1.2.15 Conclusions

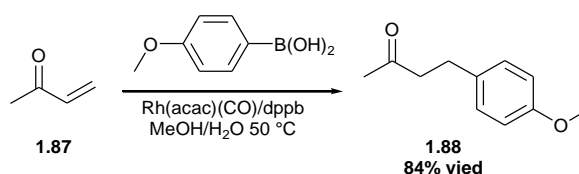
Organoboron compounds are widely established and highly utilised organometallic donors. The boron protecting groups available have expanded significantly in recent years, with different esters and ‘ate’ species offering advantageous modifications. Improvements in stability and reactivity have expanded the scope and possibilities for these reagents. Stable alkenylboronate species are now accessible and have been demonstrated as equal, if not more useful counterparts to their corresponding aryl boronates.

With a number of ‘ate’ species offering improved stability, the potassium trifluoroborate remains a protecting group of choice for alkenylboronates as it offers a balance between reagent stability and reactivity in metal catalysed reactions.

1.3 Synthetic applications of aryl organoboron reagents in the rhodium catalysed conjugate addition reaction

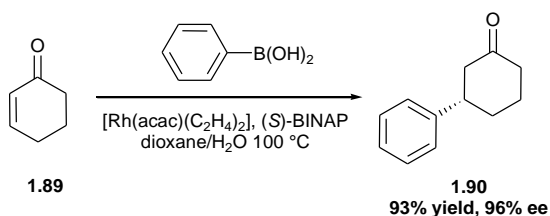
1.3.1 Introduction

Carbon-carbon bond formation is a highly desirable reaction by synthetic chemists. The rhodium catalysed conjugate addition of organoboron reagents to α,β -unsaturated carbonyl compounds is a practical method for establishing carbon-carbon bonds with predictable stereocontrol. The procedure was first published in 1997 by Miyaura and co-workers in which a range of organoboronic acids successfully underwent conjugate addition to methyl vinyl ketone **1.87** (Scheme 1.29).⁹⁵



Scheme 1.29

The first enantioselective rhodium catalysed conjugate addition followed a year later in a collaboration by Hayashi *et al.*⁹⁶ Successful enantioselective addition of organoboronic acids to 2-cyclohexenone required $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]$ as the rhodium source, (*S*)-BINAP as the chiral phosphine ligand and heating to 100°C . This achieved the desired 3-substituted cyclohexanone **1.90** in high yield and enantioselectivity (Scheme 1.30).



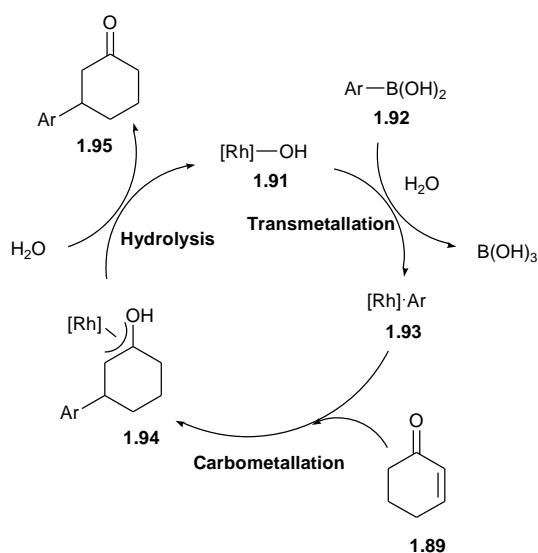
Scheme 1.30

In the initial work a range of achiral phosphine ligands, temperatures and solvents were investigated. Efficient conversion was dependent on the bite angle of the phosphine ligand. Phosphine ligands with large P-Rh-P bite angles gave higher conversions and as such $\text{dppb} > \text{dppp} > \text{TFP} > \text{dppe}$.

The reaction tolerates a wide range of functionality on both the organoboron donor and the enone. Multigram scale reactions have also been successful with high catalytic turnovers and no loss in enantioselectivity.

Important advances are continually being made to improve reaction times, enantioselectivity, catalytic loading and substrate scope, by refining the rhodium source, the base and by designing new enantiopure ligands. The leading improvements have been in the development of enantiopure diene ligands which have vastly widened the scope and enantioselectivity of the reaction.

Mechanistic studies for the rhodium catalysed conjugate addition to cyclic and acyclic activated alkenes have been conducted by Hayashi *et al.*⁹⁷ The initial step involves loss of ligands to form the active rhodium-hydroxyl precursor **1.91**. A successful catalytic cycle, as depicted in Scheme 1.31, requires transmetalation of the organoboron to rhodium to afford **1.93**, followed by co-ordination and insertion of the alkene **1.89**. Enantioselectivity is controlled by the facial selectivity of the enantiopure ligand during the carbometallation step to form an η^3 -oxa- π -allylrhodium complex **1.94**. Finally, this rhodium-enolate is protonated *via* hydrolysis to afford the product **1.95** whilst regenerating the active catalyst.

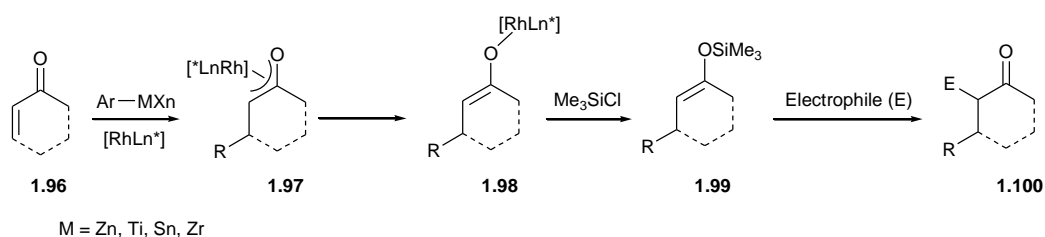


Scheme 1.31

Boronic acids are the most frequently used organoboron reagent, however an excess is required to allow for competing protodeboronation and inaccurate concentrations from trimeric cyclic anhydrides (boroxines). There are a number of elegant solutions to these problems including choosing appropriate ligands, conditions that minimise protodeboronation and the use of preformed boronates such as tris(hydroxyl)borates,⁹⁸ lithium trimethoxyboronates⁹⁹ and potassium trifluoroborates⁷⁶ for precise stoichiometry. Potassium trifluoroborate salts have been used in a number of valuable applications of rhodium catalysed conjugate addition.¹⁰⁰ When their low solubility in

organic solvents is a potential problem, it can easily be overcome by counter ion exchange from potassium to tetrabutyl ammonium.⁵¹ Alternatively, cyclic triolborates have also been highly utilised as they are equally stable, but more soluble than potassium trifluoroborates in organic solvents.¹⁰¹

Other organometallics are known to transmetallate to rhodium. Organoboron and organosilicon undergo transmetallation in the presence of water whereby hydrolysis affords the conjugate addition product and regenerates the active catalyst. However, other organometallics including organozinc, organotin, organozirconium and organotitanium donors can offer advantages in reactivity and selectivity over boron reagents and can allow other reaction pathways.¹⁰² They do not require water for catalyst turnover and transmetallation occurs at room temperature (or lower). As such, the products initially generated are metal enolates **1.98**, which can also be further functionalised by the addition of electrophiles (E) as illustrated in Scheme 1.32.



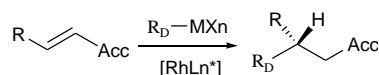
Scheme 1.32

Organoboron reagents are preferential for rhodium catalysed conjugate addition applications owing to their tolerance of water; they are easily accessible, bench stable reagents. Organoboron reagents can now replace other organometallics in more challenging reactions with less reactive acceptors owing to the expansion of enantiopure diene ligands and new boron protecting groups which have facilitated their increased stability.

Rhodium catalysed conjugate addition is an excellent tool for asymmetric synthesis and it is now possible to reliably achieve in excess of 90% ee in additions of organoboron reagents with a wide variety of acceptors.

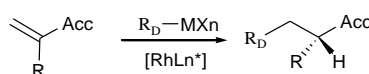
It is crucial to gain insight into the stereoselectivity issues in joining complex fragments together in order for rhodium catalysed conjugate addition to gain comparable status with the Suzuki reaction and asymmetric hydrogenations. Stereoselectivity can be introduced in a number of ways. In conjugate additions to prochiral acceptors, Scheme 1.33, a single stereocentre is introduced *via* asymmetric carbometallation controlled by an enantiopure rhodium complex. Simple stereochemical models can reliably predict the

asymmetric induction when using enantiopure diene and atropisomeric diphosphine ligands.¹⁰³



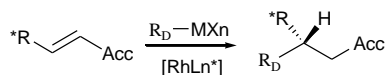
Scheme 1.33

Alternatively, in additions to 1,1'-disubstituted alkenes as shown in Scheme 1.34, the enantioselectivity is determined through enantioselective protonation, in the hydrolysis of the oxa- π -allylrhodium species.

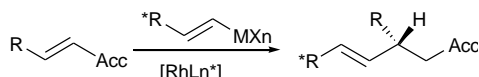


Scheme 1.34

The union of enantiopure acceptors (Scheme 1.35) and more recently enantiopure donors (Scheme 1.36), is also a useful way to introduce and control stereochemical induction.



Scheme 1.35

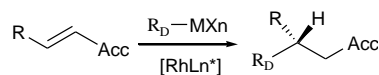


Scheme 1.36

In reviewing rhodium catalysed conjugate additions, the most relevant examples are in the application of the reaction towards complex molecular synthesis and biologically active compounds.¹⁰⁴ These not only illustrate the usefulness and scope of the procedure, but also highlight issues concerning reactivity and selectivity.

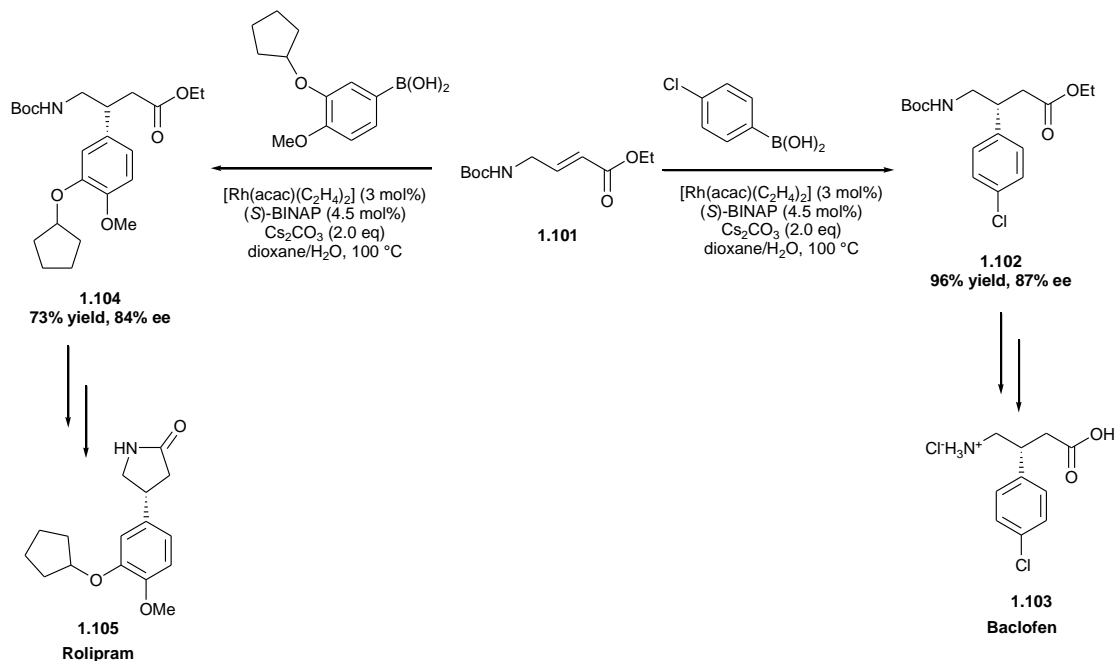
1.3.2 Prochiral acceptors

The most common cases of conjugate addition are to prochiral acceptors, where a single stereocentre is induced through asymmetric carbometallation, controlled by an enantiopure rhodium complex, as shown in Scheme 1.37. Enantiopure atropisomeric diphosphine and enantiopure diene ligands are required and simple stereochemical models can reliably predict their stereochemical outcome.



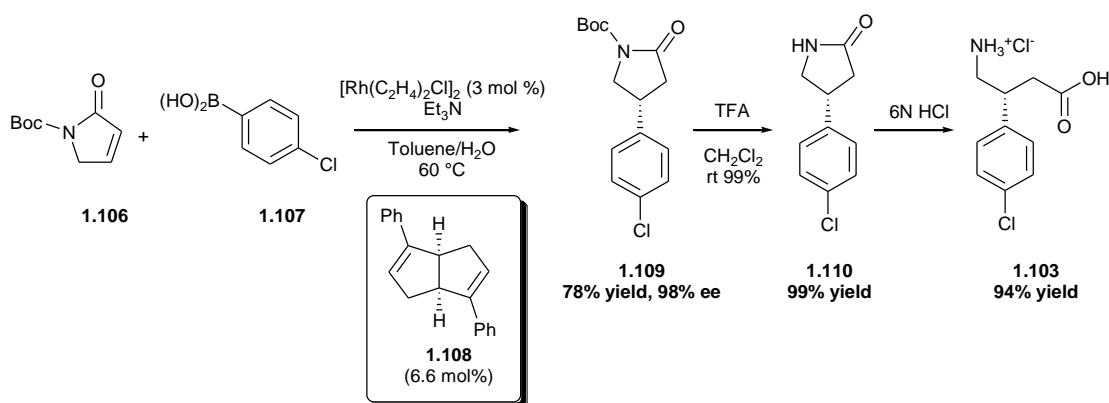
Scheme 1.37

Early applications of rhodium catalysed conjugate addition were towards pharmaceutical agents Baclofen¹⁰⁵ (**1.103**) and Rolipram¹⁰⁶ (**1.105**). Helmchen and co-workers reported conditions requiring the conjugate addition to α,β -unsaturated- γ -aminobutyric ester **1.101** utilising (*S*)-BINAP to achieve 87% ee and 84% ee respectively (Scheme 1.38).



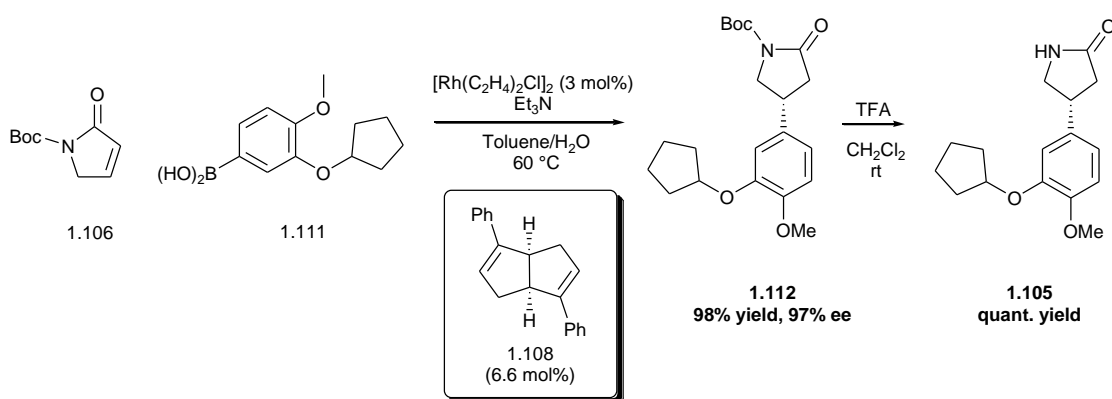
Scheme 1.38

More recently their synthesis has been achieved through conjugate addition to α,β -unsaturated lactams using enantiopure diene **1.108**, as shown in Scheme 1.39.¹⁰⁷ Enantiopure diene ligands have offered a number of advantages over phosphine ligands, including higher reactivities and enantioselectivities for a number of rhodium catalysed asymmetric reactions.^{108, 109, 110} It is not surprising therefore that enantioselectivities have been increased to 99% through the use of enantiopure diene ligands and that direct addition to γ -lactam **1.106** has also been facilitated. This has enabled a much shorter total synthesis of both Baclofen **1.103** and Rolipram **1.105**. Lin and co-workers' optimised conditions for the rhodium catalysed conjugate addition also require triethylamine in toluene/water at 60 °C and highlight that KHF₂ is a useful additive to improve yields for rapidly hydrolysed electron deficient boronic acids.

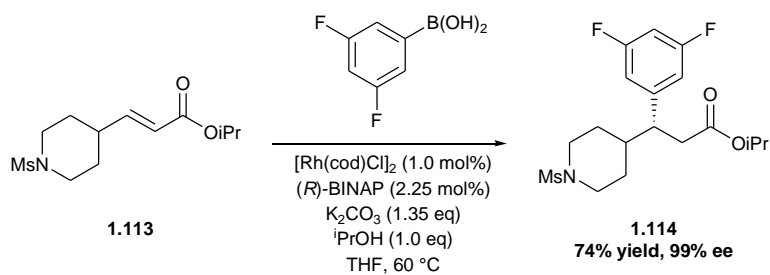


The β -substituted- γ -lactams including **1.109**, are direct precursors to biologically active compounds with excellent enantioselectivity. For example, after the addition of *p*-chlorophenylboronic acid, two further steps involving BOC deprotection followed by hydrolysis using 6N HCl are necessary to generate GABA_B receptor agonist (*R*)-baclofen hydrochloride **1.103**.

Similarly, antidepressant (*R*)-Risperidone is accessible in just two steps by subsequent TFA deprotection of the addition adduct **1.112** (Scheme 1.40).



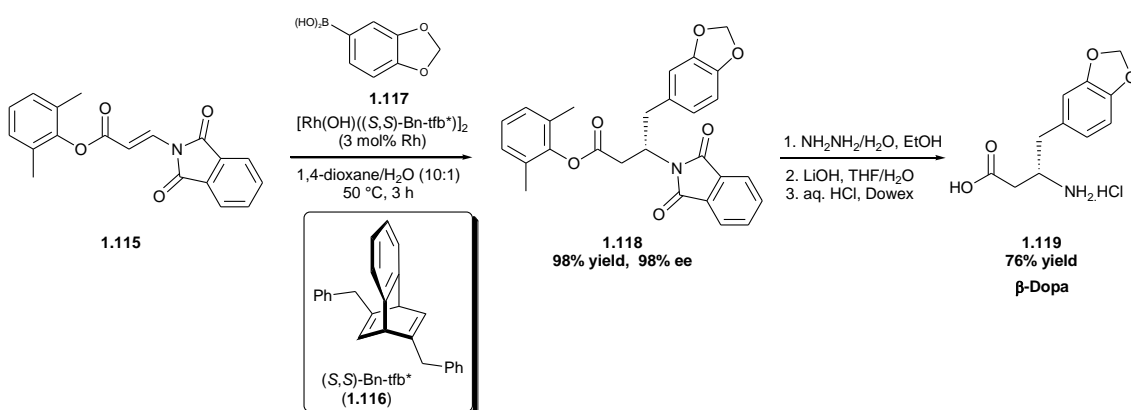
A kilogram-scale enantioselective conjugate addition has been developed by Parker and co-workers at AstraZeneca, as part of a drug development program. They completed two 27 kg batches of boronic acid addition to alkene **1.113** to access more than 50 kg of desired product with excellent stereocontrol using commercially available (*R*)-BINAP (Scheme 1.41).¹¹¹



Scheme 1.41

They have addressed a number of scale-up issues including protodeboronation, base insolubility and removal of rhodium from the product. They have reduced protodeboronation by replacing water with a minimal amount of isopropanol, which allowed for a significant reduction in the amount of arylboronic acid needed. The rhodium content in the final product has been reduced to less than 30 ppm by using an oxidant and a scavenger.

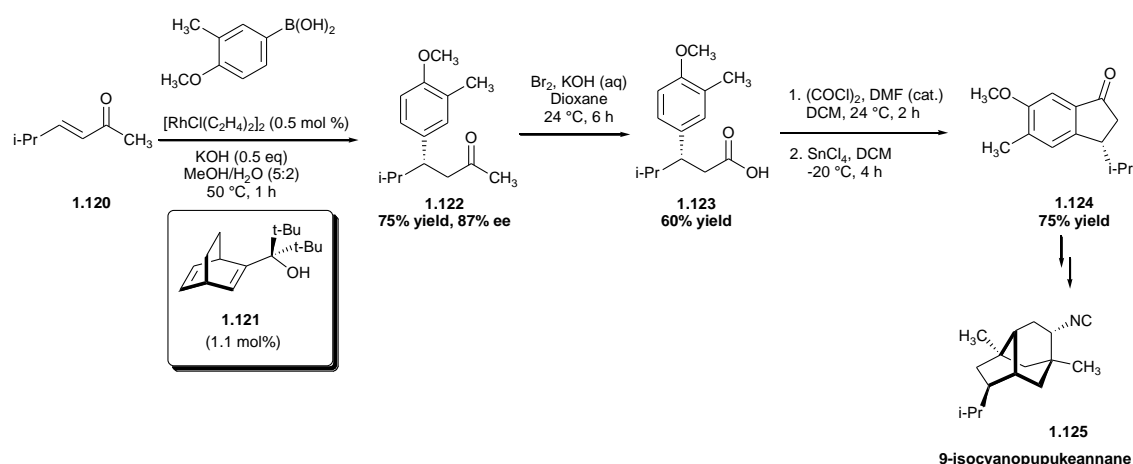
A number of β -substituted- β -amino acids are readily accessed through enantioselective 1,4-addition of boronic acids to β -phthalimidoacrylate esters.¹¹² Optimised conditions employ the catalyst [Rh(OH)((*S,S*)-Bn-tfb*)]₂ containing enantiopure diene **1.116**, which delivers high yielding products with high enantioselectivities. This elegant methodology was utilised within a concise synthesis of (*R*)- β -dopa and other β -amino acids. The addition of boronic acid **1.117** to β -phthaliminoacrylate ester **1.115** afforded product in 98% ee. Subsequent deprotection of the phthaloyl group using hydrazine, followed by basic hydrolysis of the ester completed the synthesis of (*R*)- β -dopa as the hydrochloride salt **1.119** (Scheme 1.42).



Scheme 1.42

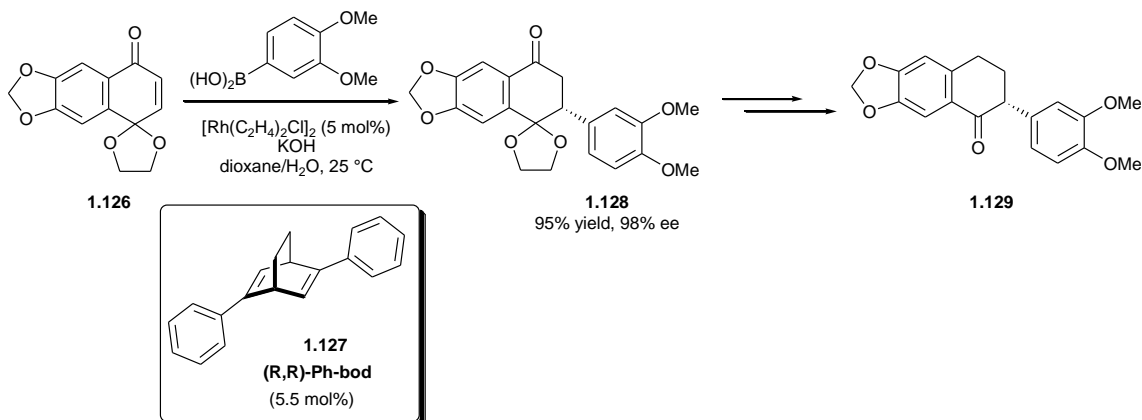
The key intermediate **1.124** in the synthesis of 9-isocyanopupekeannane **1.125** has been synthesised *via* rhodium catalysed conjugate addition.¹¹³ Good enantioselectivities are achieved by employment of a new enantiopure bicyclooctadiene-based ligand **1.121** as

described in Scheme 1.43. A series of similar enantiopure ligands were also described by Corey and co-workers in this paper using highly enantioselective Diels-Alder methodology.



Scheme 1.43

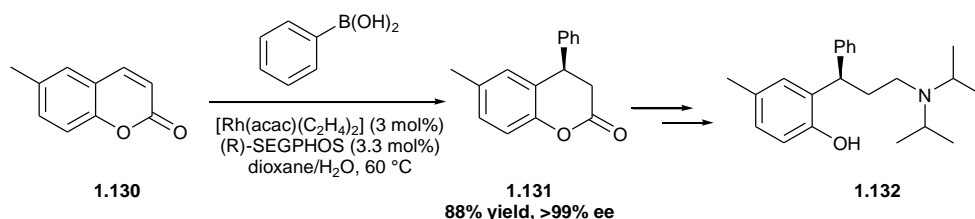
A novel approach towards 2-aryltetralones has been achieved using rhodium catalysed conjugate addition to complete a formal α -arylation (Scheme 1.44).¹¹⁴ Despite the need for a high catalytic loading, the addition of 3,4-dimethoxyphenylboronic acid proceeds at room temperature. The bulky ethylene ketal moiety adjacent to the β -position of the enone is well tolerated and the desired product (**1.128**) is achieved in high enantioselectivity. Four subsequent reactions using standard conditions achieve the α -substituted ketone **1.129**, which is a key intermediate in the synthesis of hexahydrobenzo[c] benzophenanthridine alkaloids.



Scheme 1.44

The rhodium catalysed conjugate addition of boronic acids to coumarin derivative **1.130** in Scheme 1.45, afforded 4-arylchroman-2-ones such as **1.130**, where the β -stereogenic carbon centre is substituted with two aryl groups.¹¹⁵ This functionality is particularly

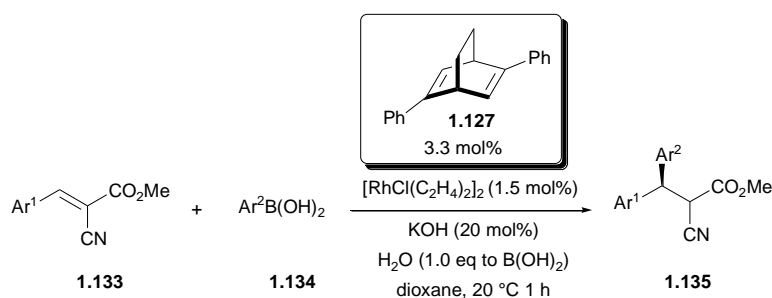
prevalent in pharmaceutical agents and natural products including an important urological drug (*R*)-tolterodine **1.132**.



Scheme 1.45

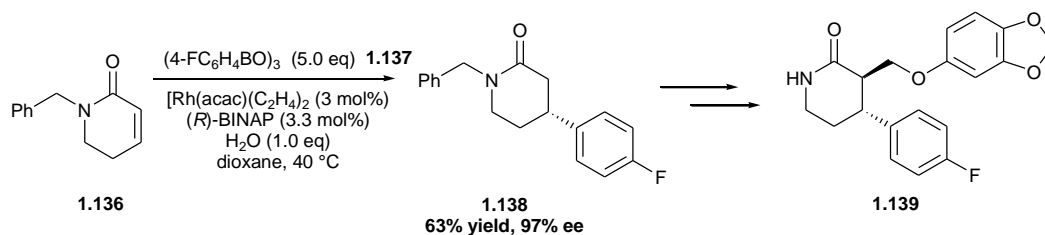
(*R*)-SEGPHOS was employed in the asymmetric conjugate addition successfully giving high enantioselectivities. However, as coumarins tend to be relatively poor substrates for conjugate additions, up to ten equivalents of boronic acid donor were required for successful conversion. The route towards (*R*)-tolterodine uses (*R*)-6-methyl-4-phenylchroman-2-one **1.131** formed *via* conjugate addition. The reduction of the lactone to the lactol is followed by palladium catalysed hydrogenation in the presence of diisopropylamine to yield 91% of the final product.

More recently, (*R*)-Tolterodine has been synthesised by conjugate addition to arylmethylene cyanoacetates (**1.133**) catalysed by rhodium enantiopure diene complex (*R,R*)-Ph-bod (**1.127**).¹¹⁶ Despite a more lengthy total synthesis to this particular drug, the products (**1.135**) generated directly from conjugate addition consist of the important β,β -diaryl- α -alkyl functionality (Scheme 1.46). This is further demonstration of enantiopure diene ligands expanding the range of α,β -unsaturated acceptors that can be reacted successfully under conjugate addition conditions.



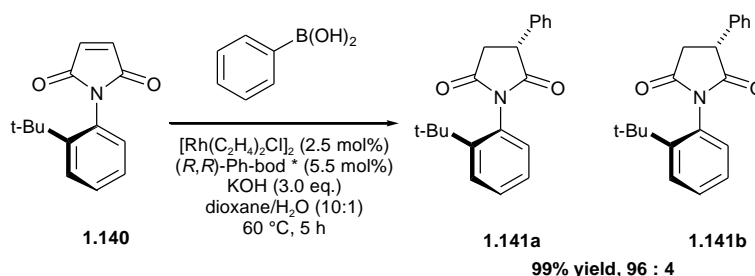
Scheme 1.46

An early application of rhodium catalysed conjugate addition employed boroxine **1.127** and BINAP.¹¹⁷ Successful addition to 5,6-dihydro-2-(1*H*)-pyridinone **1.136** afforded a key intermediate in the synthesis of Paroxetine, an anti-depressant and anti-Parkinson's drug (Scheme 1.47).



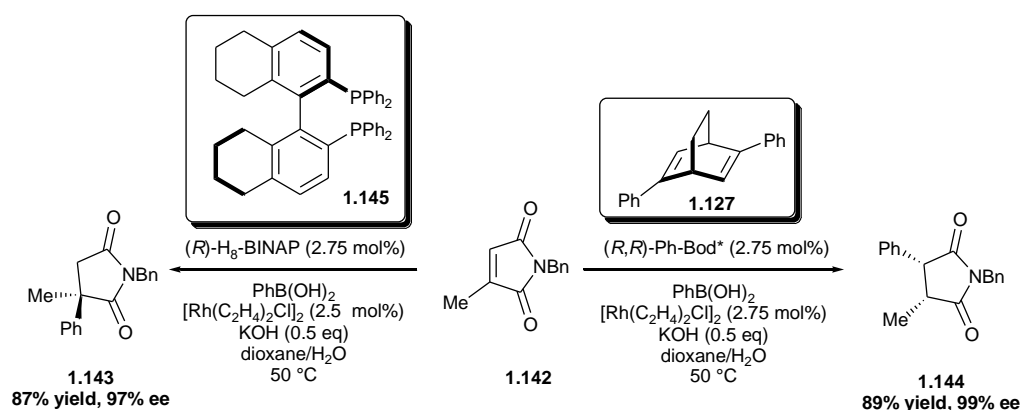
Scheme 1.47

Maleimides have proved to be effective substrates for conjugate additions.^{118, 119} Asymmetric rhodium catalysed conjugate addition of arylboronic acids to N-aryl maleimides constructs chiral C–N axes.¹²⁰ Scheme 1.48 below, highlights how both central and axial chiralities were controlled simultaneously to afford a 96 : 4 ratio of **1.141a**:**1.141b** by employing Rh/(*R,R*)-Ph-bod* as a catalyst. The high levels of selectivity observed can be attributed to the steric hindrance between the *tert*-butyl group on maleimide **1.140** and the enantiopure diene ligand which leads to specific coordination around the metal centre. Interestingly, the employment of other ligands such as (*R*)-BINAP or phosphoramidites led to much lower levels of stereoselectivity.



Scheme 1.48

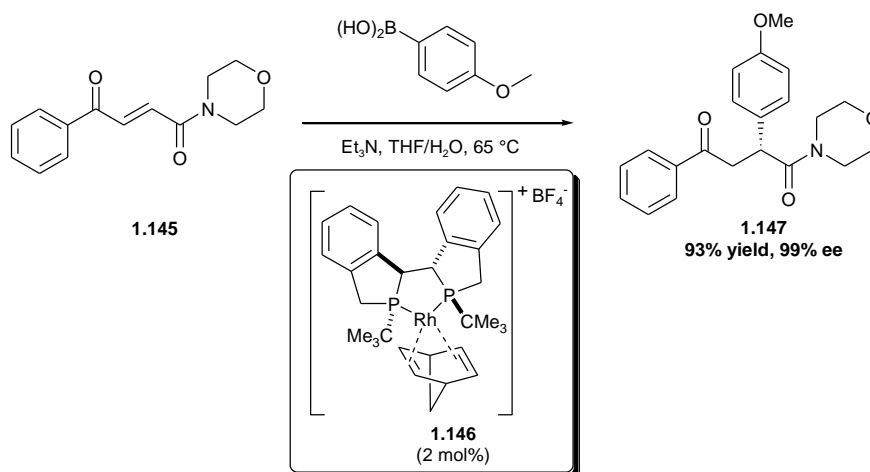
The enantioselective construction of all carbon quaternary centres is an important challenge in rhodium catalysed conjugate additions. Hayashi and co-workers have successfully developed an enantioselective conjugate addition of arylboronic acids to 3-substituted maleimides **1.142**, furnishing 3,3'-disubstituted succinimides in high regio- and enantioselectivity.¹²¹ The reaction displays an interesting ligand effect whereby (*R*)-H₈-BINAP **1.145** preferentially forms the quaternary 3,3'-disubstituted product **1.143** while enantiopure diene (*R,R*)-Ph-Bod* **1.127** generates 2,3-bis-substituted product **1.144** as illustrated by Scheme 1.149.



Scheme 1.49

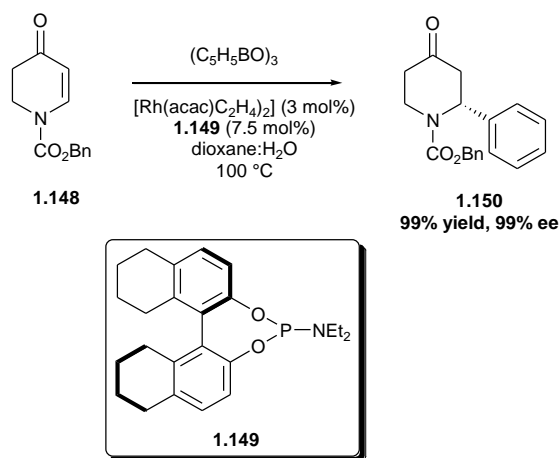
Quaternary carbon centres can be efficiently constructed by the rhodium catalysed conjugate addition of sodium tetraarylboronates to β,β -disubstituted- α,β -unsaturated carbonyl compounds. Once again, enantiopure diene ligands such as (R,R) -Bn-bod* and (R,R) -Ph-bod* are required to achieve good reactivity and high enantioselectivity.⁴⁴

In contrast to maleimides, orthogonally substituted α,β -unsaturated compounds such as oxobutenamides **1.145**, present a synthetic challenge in conjugate addition chemistry to overcome regioselectivity issues. The conjugate addition of organoboronic acids to oxobutenamides requires a catalyst system that not only distinguishes enantiotopic π -faces, but also the subtle electronic differences of each conjugate acceptor. Faul and co-workers have accomplished this using a rhodium-Duanphos complex **1.146**.¹²² The conditions were optimised as shown in Scheme 1.50, with this sterically bulky chiral phosphine ligand to deliver the desired (R) -2-(4-methoxyphenyl)-1-morpholino-4-phenyl butane-1,4-dione regioisomer **1.147** in excellent enantioselectivity.



Scheme 1.50

Feringa et al. have shown that enantiopure phosphoramidite ligands, such as **1.149**, provide excellent selectivity in the addition of organoboronic acids and organoboroxines to piperidones **1.148** (Scheme 1.51).¹²³

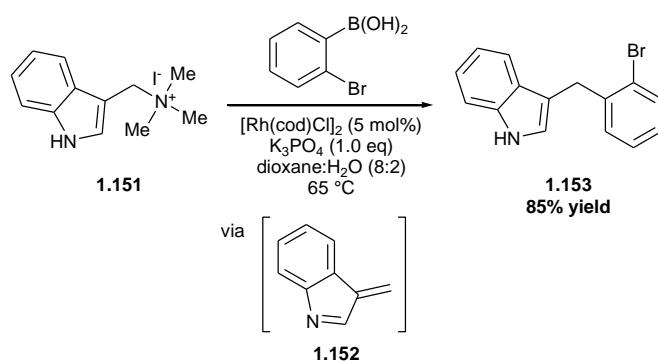


Scheme 1.51

Although piperidones are not as reactive as other cyclic unsaturated carbonyl compounds, reactions still proceed with high yields and selectivity. Boronic acids could be employed successfully, but their conversions were limited to 80%. This was overcome by utilising phenyl boroxine with slow addition of water to give the product in high yields whilst retaining high enantioselectivity.

More reactive heteroarylzinc and heteroaryl titanium donors are frequently reported to undergo similar challenging transformations in higher yields and with excellent enantioselectivity.¹²⁴ This is of particular benefit to less reactive substrates such as Meldrum's acid¹²⁵ and cyclic lactones (5,6-dihydro-2*H*-pyran-2-one).

Gramines (3-aminomethylindoles) can also be used in conjugate addition reactions, but through a tandem procedure.¹²⁶ At high temperatures these compounds readily undergo retro-Mannich reactions for *in situ* formation of the alkene able to undergo nucleophilic addition. Csáky and co-workers have demonstrated this by quaternising the amino group into the trimethyliodide species as in **1.151**. Consequently, as illustrated in Scheme 1.52, benzylic substitution of indoles is possible through the tandem retro-Mannich conjugate-addition which occurs in high yields.

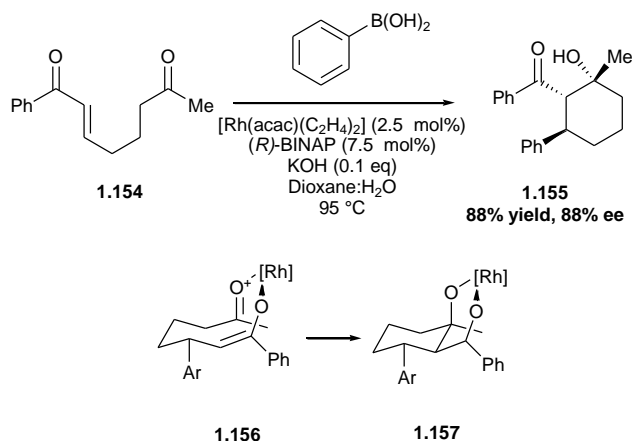


Scheme 1.52

Tandem or domino rhodium catalysed conjugate addition reactions have emerged as useful tools for efficient organic synthesis including enantioselective processes.^{127,128,129}

In this context, there have been a number of efficient processes reported where a rhodium catalysed conjugate addition generates an organorhodium(I) intermediate that can participate in a subsequent intramolecular reaction with a number of functional groups, including imines,¹³⁰ nitriles,¹³¹ alkynes,¹³² ketones¹³³ and enones.¹³⁴

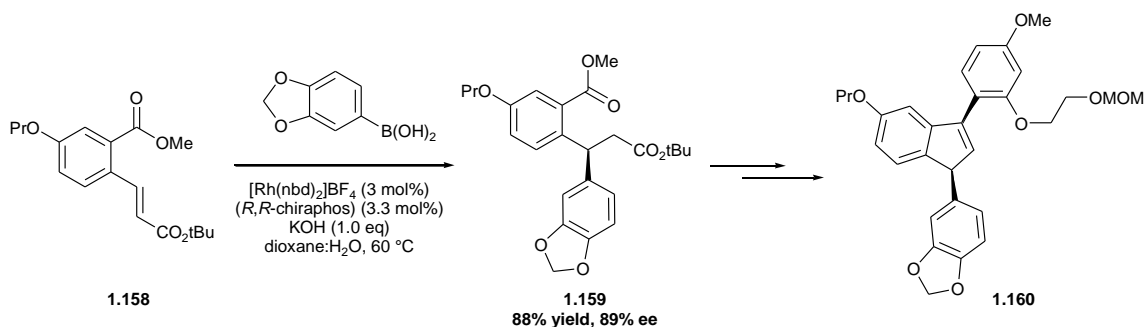
An elegant example by Krische *et al.* is the intramolecular domino conjugate addition-aldol reaction of boronic acids with enone-ketones (Scheme 1.53).¹³⁵ The intramolecular reaction with the ketone is faster than protonolysis with water and therefore the cyclisation product **1.155** is formed, even in the presence of water. Enantiopure (*R*)-BINAP was found to be the ligand of choice and the stereochemistry observed for the aldol reaction can be accounted for by the Zimmerman–Traxler type transition state of the (*Z*)-enolate **1.156**. This methodology has been extended to the synthesis of bicyclic structures with excellent diastereo- and enantioselectivity.¹³³



Scheme 1.53

Miyuara and co-workers have used a similar, but step-wise approach in the enantioselective synthesis of endothelin receptor antagonists (Scheme 1.54).¹³⁶ Use of (*R,R*)-chiraphos as enantiopure ligand in conjunction with $[\text{Rh}(\text{nbd})_2][\text{BF}_4]$ enabled the

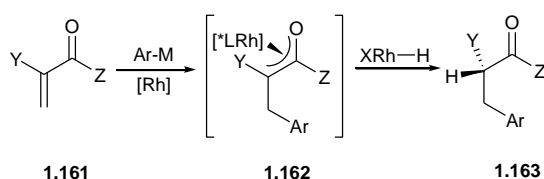
conjugate addition of boronic acid to functionalised acrylate acceptor **1.158** which afforded product **1.159** in 89% ee. A number of subsequent synthetic steps transformed the addition product to key endothelin antagonist intermediate **1.160**.



Scheme 1.54

1.3.3 Enantioselective protonation

The asymmetric arylation of activated alkenes or allenes *via* enantioselective protonation is an interesting and challenging variant of the typical rhodium catalysed addition process.¹³⁷ Reaction of a 1,1'-disubstituted alkene **1.161** with an arylrhodium species forms a chiral π -allylrhodium intermediate which undergoes enantioselective protonation to generate the product enantioselectively (Scheme 1.55).



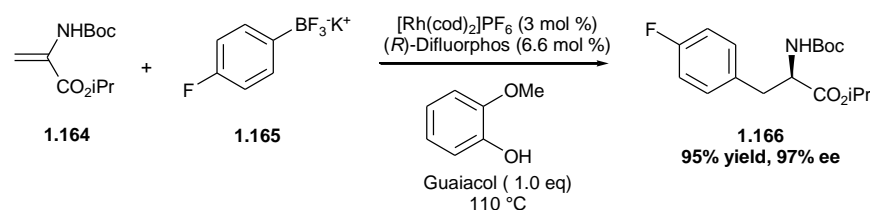
Scheme 1.55

Amino acids are of obvious synthetic and biological interest. Both α and β -amino acids have been synthesised using this conjugate addition-enantioselective protonation methodology.

Initial applications involved enantioselective rhodium catalysed additions of boronic acids to α,β -dehydroamino acid derivatives. The process enabled access to a wide range of substituted phenylalanine α -amino acids, but only modest enantioselectivities were achieved.¹³⁸

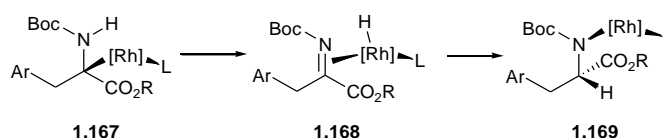
Potassium trifluoroborate salts have produced significant advances in the asymmetric synthesis of α -amino acids *via* the tandem 1,4-addition/enantioselective protonation reaction.¹³⁹ Studies by Darses and co-workers also highlight improved enantioselectivity through the use of alternative proton sources to water. Following a screen of various

proton sources it emerged that *ortho*-substituted phenols, in particular 2-methoxyphenol (guaiacol), produced high selectivities as illustrated in Scheme 1.56.



Scheme 1.56

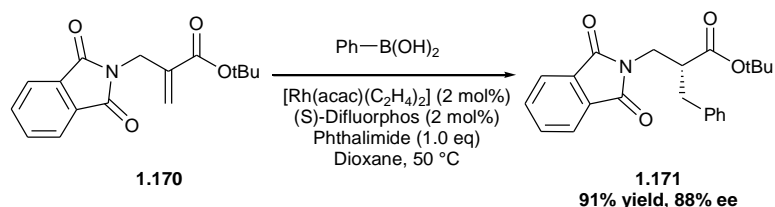
The phenol could be recovered easily and quantitatively after the reaction by simple acidification/extraction procedures. Interestingly, under the described conditions protodeboronation was not observed. The high levels of enantioselectivity can be explained by an alternative mechanism proposed by Darses *et al.* as shown in Scheme 1.57. Following further studies they suggest a hydride transfer occurs from the amido group to the α -carbon.



Scheme 1.57

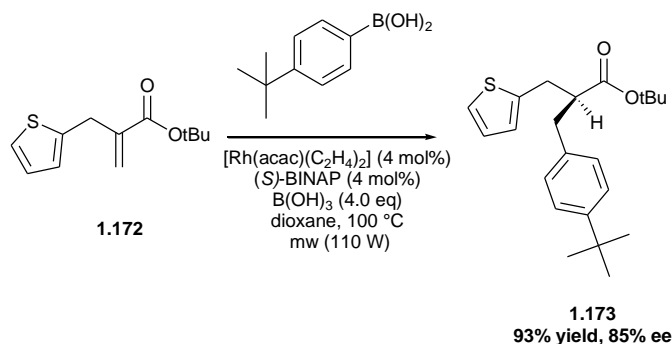
Frost and co-workers have also studied the domino addition/protonation reaction. The cationic rhodium catalyst $[\text{Rh}(\text{COD})_2][\text{PF}_6]$ and *(R)*-BINAP were employed for additions to dimethylitaconate, where water was revealed as the optimum proton source for high enantioselectivity.¹⁴⁰ This highlights the sensitivity of this reaction to variations in substrate and conditions.

Rhodium catalysed conjugate addition has also been used to synthesise β -amino acids from β -amino acrylates. Sibi *et al.* has expanded existing racemic methodology in the synthesis of β^2 -amino acids in up to 91% ee using phthalimide as a proton source.¹⁴¹ The greatest enantioselectivity is achieved when the bulky *tert*-butyl ester group is used in combination with the phthalimide nitrogen protecting group. Scheme 1.58 shows the addition of phenylboronic acid to substrate **1.170** for the enantioselective synthesis of protected β^2 -amino acid **1.171**. A number of boronic acids have been applied successfully, however the yields are variable.



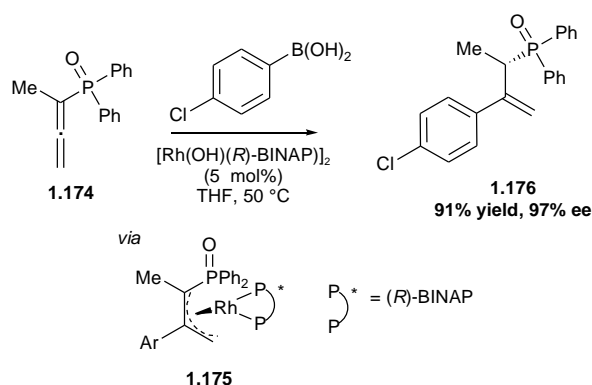
Scheme 1.58

Similarly, enantiomerically enriched α,α' -dibenzyl esters have been prepared using tandem rhodium catalysed conjugate addition-enantioselective protonation. The required α -benzyl acrylates can be easily accessed from the corresponding aldehydes. Under microwave conditions, the highest enantioselectivity was achieved by combining boric acid as a proton source and BINAP as the enantiopure ligand.¹⁴² For example, Scheme 1.59 illustrates the successful addition to thiophene substituted *tert*-butyl acrylate **1.172** in reasonable enantioselectivity to afford product **1.173**.



Scheme 1.59

Diphenylphosphinylallenes, such as **1.174**, are also effective substrates for rhodium catalysed conjugate addition-protonation. Hayashi *et al.* reported the use of preformed rhodium–BINAP catalyst $[\text{Rh}(\text{OH})(\text{R})\text{-BINAP}]$ to complete successful hydroarylation with arylboronic acids in up to 98% ee (Scheme 1.60).¹⁴³ The reaction also yielded significant quantities of the reduced product which could be minimised by replacing 1,4-dioxane with THF. The stereochemical outcome of this reaction implies that, as with the addition to acrylates, protonation occurs from the same face as the rhodium on the thermodynamically stable π -allylrhodium intermediate **1.175**. However, it is worth noting that the proton source for this reaction is the boronic acid itself, rather than a further reagent.



Scheme 1.60

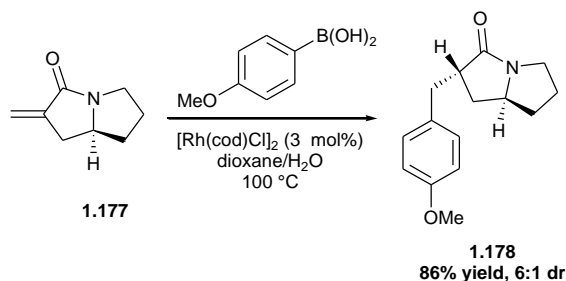
An interesting variation of tandem conjugate addition/protonation is rhodium catalysed conjugate addition halogenation whereby electrophilic halogen sources are used in place of the proton source.¹⁴⁴

1.3.4 Enantiopure acceptors

A further way to introduce and control stereochemistry in the rhodium catalysed conjugate addition reaction is through the employment of enantiopure acceptors. The increasing number of applications involving enantiopure acceptors highlights the remarkable synthetic potential of the reaction.

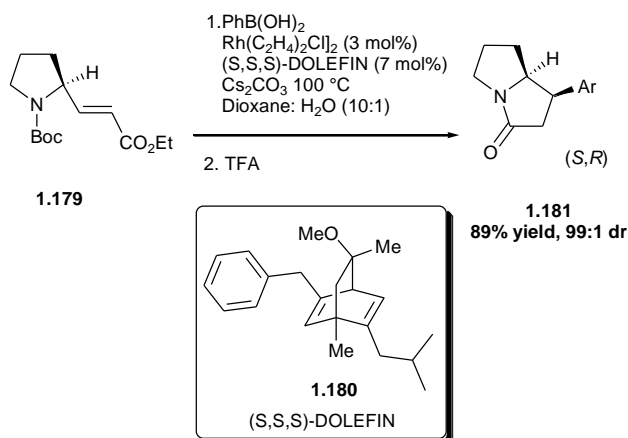
Key examples by Frost and co-workers demonstrate conjugate addition to enantiopure acceptors derived from (*S*)-proline in convenient stereoselective routes to different functionalised pyrrolizidinones. The products generated are valuable precursors of compounds related to pyrrolizidine alkaloids.

The first process involves conjugate addition of boronic acids to an enantiopure bicyclic lactam 1.177 producing 2-substituted pyrrolizidinones 1.178, with (2*S*,7*S*) being the major stereoisomer (Scheme 1.61).¹⁴⁵ For efficient transmetallation, a high temperature and the presence of water are both necessary.



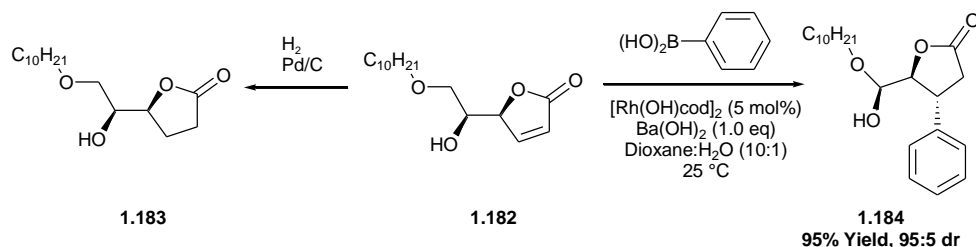
Scheme 1.61

Alternatively, the second stereoselective route utilises a different enantiopure acceptor **1.179**, again derived from (*S*)-proline.¹⁴⁶ Conjugate addition is followed by boc deprotection and lactamisation to generate pyrrolizidinones **1.181** in high yields (Scheme 1.62). In this case, the enantioselectivity of the conjugate addition is amplified through ligand control where the highest selectivity was observed by utilising commercially available chiral bicyclo-[2.2.2]octadiene (DOLEFIN) ligands (**1.180**). The matched (*S,S,S*)-ligand gave the (*S,R*)-diastereomer in excellent diastereoselectivity.



Scheme 1.62

Another class of compounds which can be obtained efficiently using conjugate addition are β -substituted chiral δ -hydroxy- γ -butanolides, including β -substituted analogues of the antitumour compound (-)-7-oxamuricatacin **1.183**. The chiral hydroxyl group enables high diastereoselective control in the addition reaction of aryl boronic acids; owing to steric hindrance the nucleophile is forced to approach from the opposite face to selectively afford the 3,4-*trans* isomer. Thus as depicted in Scheme 1.63, the conjugate addition of phenyl boronic acid to butenolide **1.182** delivers analogue **1.184** with excellent *trans* diastereoselectivity and high yield.¹⁴⁷

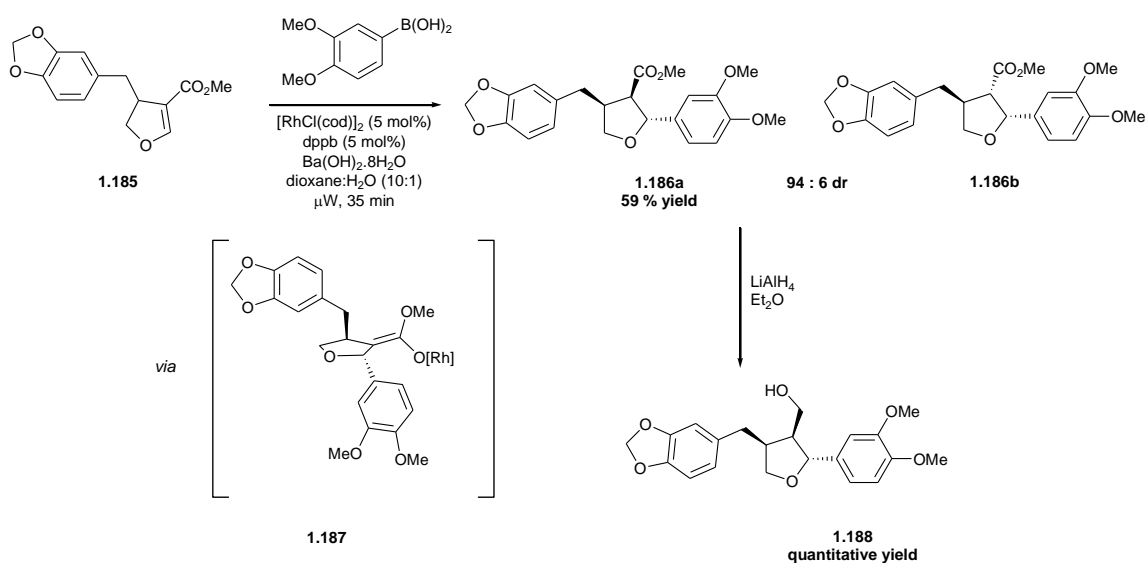


Scheme 1.63

Trisubstituted furanolignans have been synthesised using rhodium catalysed conjugate addition of aryl boronic acids to unsaturated furano esters as the key step to selectively direct three contiguous stereocentres.¹⁴⁸ Although the acceptor is not chiral it offers

substrate control similar to that of enantiopure acceptors such that no enantiopure ligand is required. The stereoselectivity is achieved *via* steric controlled addition of the aryl metal species to the least hindered face of the dihydrofuran. Therefore directing the stereogenic centres C2 and C4 to the desired configuration.

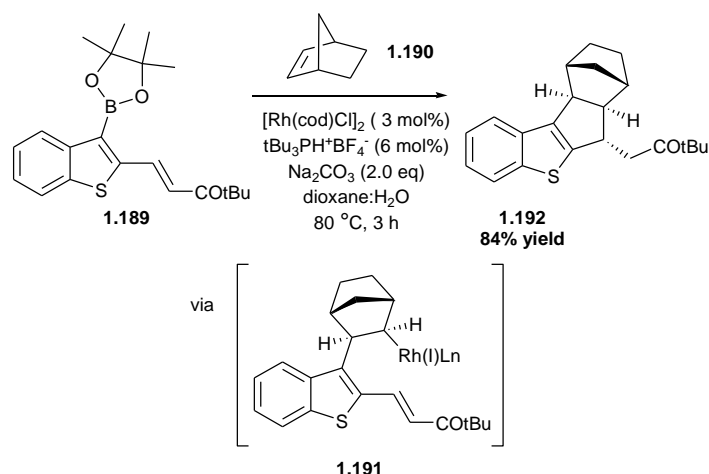
Microwave conditions were employed for the addition which proceeds with excellent diastereoselectivity such that only two epimers **1.186a** and **1.186b** are formed in 94:6 dr with the major isomer having the desired configuration. Reduction of the products with LiAlH_4 completed the total synthesis of the natural 2,3,4-trisubstituted lignans (Scheme 1.64).



Scheme 1.64

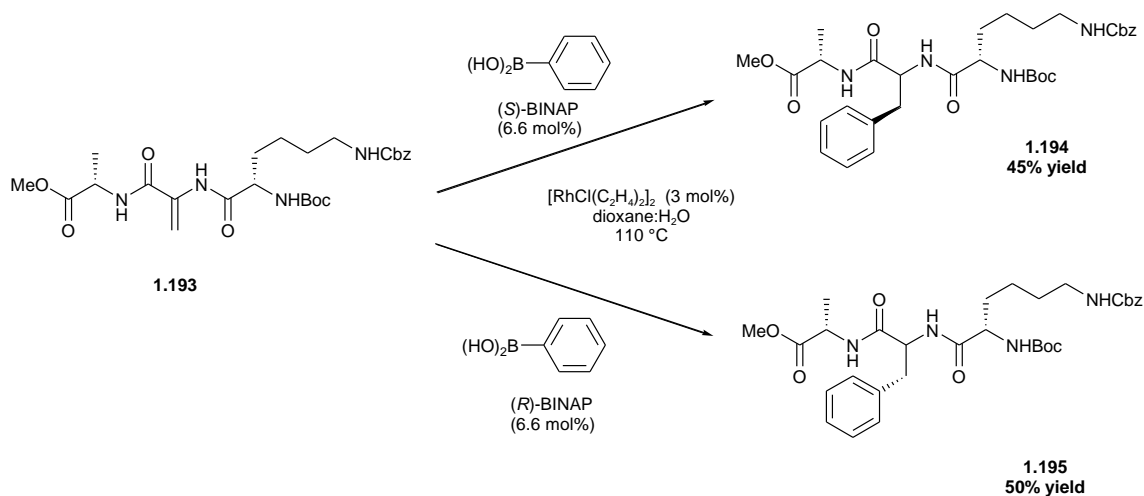
Similar control of contiguous stereocentres is also possible where conjugate addition has been employed in tandem processes such that the oxa- π -allyl rhodium species sequentially reacts with a second functional group.

A recent example is the synthesis of biologically active polycyclic heteroaromatic compounds *via* a rhodium catalysed addition/cyclisation cascade.¹⁴⁹ *Ortho*-functionalised heteroaromatic boronic ester **1.189** undergoes successful reaction with strained alkene **1.190** in excellent yield (Scheme 1.65). The stereochemical outcome of the reaction is determined through *exo*-carborhodation and sequential diastereoselective cyclisation *via* intermediate **1.191**.



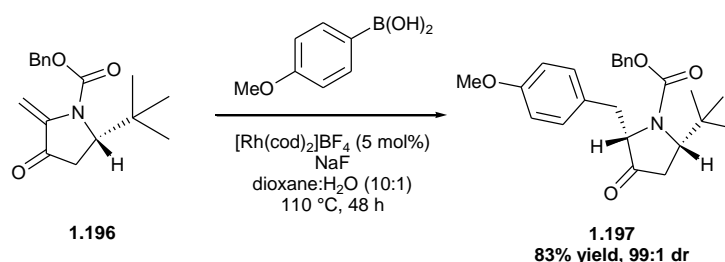
Scheme 1.65

Frost and co-workers have reported a significant application of rhodium catalysed conjugate addition in the highly desirable modification of peptides. Dehydroalanine residues, accessed through activation and β -elimination of serine or cysteine residues, are desirable acceptors for conjugate addition reactions providing a convenient strategy for incorporating unnatural phenylalanine derivatives.¹⁵⁰ The strategy was employed to generate analogues of urotensin. The dehydroalanine tripeptide **1.193** was formed by dehydration of the serine residue of the tripeptide Boc-Lys(Cbz)-Ser-Ala-OMe and subsequently underwent rhodium catalysed conjugate addition with phenylboronic acid under standard conditions (Scheme 1.66). (*S*)-BINAP provided 45% yield of *D*-phenylalanine adduct **1.194**, whilst (*R*)-BINAP afforded 50% yield of *L*-phenylalanine addition product **1.195**. Successful incorporation of other functionalised aryl groups highlights the utility of this method for late stage modification of peptides and complex organic molecules.



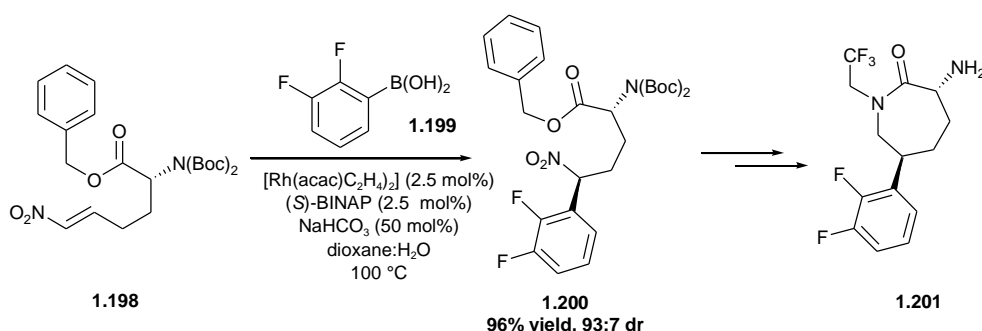
Scheme 1.66

More recently Frost and co-workers have presented the rhodium catalysed conjugate addition of aryl boronic acids to enantiopure oxazolidinone scaffolds (**1.196**) to gain access to functionalised phenylalanine derivatives (Scheme 1.67). The addition is highly stereoselective whereby the oxazolidinone template controls the protonation with perfect stereocontrol. The rhodium-aryl complex associates to the oxazolidinone *anti* to the *tert*-butyl group, on the least hindered face. The proton source pre-coordinates to rhodium and therefore also adds *anti* to the bulky *tert*-butyl group to selectively generate the *syn* diastereomer **1.197**.¹⁵¹



Scheme 1.67

The multistep synthesis of (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-azepan-2-one (MK-0974, **1.201**), an antagonist for the treatment of migraines, has been completed utilising rhodium catalysed conjugate addition as a key step.¹⁵² The addition of arylboronic acid **1.199** to nitroalkene **1.198** occurs in high diastereoselectivity. Under standard literature conditions employing $[\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2]/\text{BINAP}$ at 100 °C in dioxane/water, the boronic acid rapidly protodeboronates. However, by decreasing the temperature to 45 °C and increasing the catalytic loading, the desired intermediate was isolated in excellent yield (Scheme 1.68).



Scheme 1.68

1.3.5 Conclusions

The rhodium catalysed conjugate addition of organoboron donors has clearly become a practical tool for the assembly of drug discovery intermediates and complex molecules. Many previous issues in reactivity and stereoselectivity of complex fragments have been overcome with the significant introduction and development of enantiopure diene ligands. It is evident this valuable reaction is continually progressing in the expansion of complexity of donors and acceptors, as part of multicomponent reactions and in the ability to modify complex substrates such as peptides. Multigram applications are increasing, again demonstrating the importance and commercial value of the reaction. Scale up issues, such as protodeboronation have therefore begun to be addressed, although challenges remain in being able to apply alkenylboronic acids with the same success.

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Chapter 2: Synthetic routes to potassium alkenyl trifluoroborate salts

2.1 Chapter overview: Potassium alkenyl trifluoroborate salts are stable organometallic reagents. They are highly desirable for application in the rhodium catalysed conjugate addition reaction. However, at present only a handful of simple and unfunctionalised examples are commercially available. A library of functionalised potassium alkenyl trifluoroborate salts would be useful to explore their application in the rhodium catalysed conjugate addition reaction in order to address issues with isomerisation and protodeboronation.

2.2 Aims: To synthesise a library of novel achiral and enantiopure potassium (*E*)-alkenyl trifluoroborate salts which have the potential to construct natural and novel products. Hydroboration strategies will be employed with functionalised, achiral and enantiopure alkynes.

2.3 Standard synthesis

2.3.1 Introduction

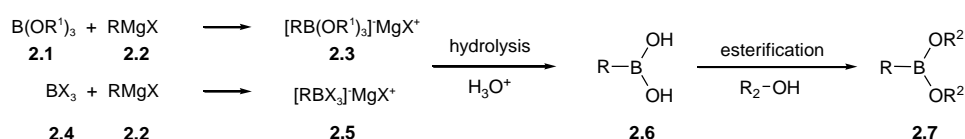
Potassium trifluoroborate salts have an enormous synthetic potential across a wide variety of areas within chemistry, most notably as donors in metal catalysed coupling reactions. However, their commercial availability and functionality is limited. An array of synthetic strategies now exist that would enable access to potassium alkenyl trifluoroborates; traditional methods involve standard hydroboration of alkynes whilst in recent years transition metal catalysis has been used to control hydroboration and also facilitate alkene borylation. With the aim of employing alkenylboronates in synthetic applications, it would seem reasonable that we would need a library of novel potassium alkenyl trifluoroborate salts, with a variety of functionality to test the scope of reactions. Application of available methods to generate a library of novel potassium alkenyl trifluoroborate salts demonstrates the ease of accessibility of this class of reagent.

2.3.2 Synthesis of alkenylboronates

As previously discussed it is now possible to expand the range of alkenylboronates available by manipulation of alkenyl potassium trifluoro, MIDA and DAN protected organoboron compounds. Whilst this area of synthesis is currently expanding, still remaining is the introduction of boron. The most common method for the introduction

of boron is hydroboration, but over time new methods have been developed including catalytic hydroboration, dehydrogenative hydroboration and metathesis.

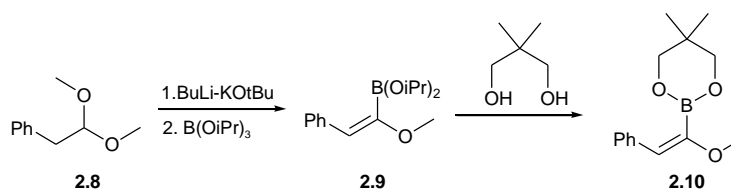
The first alkenyl boronic acid to be reported was β -styreneboronic acid in 1939.¹ It was synthesised by reacting β -styrylmagnesium bromide with isobutyl borate.² Thus many early boronates were synthesized *via* transmetallation of Grignard reagents and either trialkoxyboranes (**2.1**) or trihaloboranes (**2.4**) (Scheme 2.1).³ Subsequent hydrolysis leads to boronic acids (**2.6**) which can be esterified with alcohols, or more preferably diols, to form boronic esters (**2.7**).



Scheme 2.1

With the discovery of alkenyllithium preparation from alkenylbromides, alkenyl boronates were also synthesised from alkenyllithium species.² This was particularly useful where Grignard reagents were either unsuccessful or unavailable.

Triisopropylborate is an excellent reagent for trapping lithium intermediates and can easily be transesterified. This methodology has been used to synthesize alkoxy-functionalised alkenylboronic esters such as **2.10** (Scheme 2.2).⁴



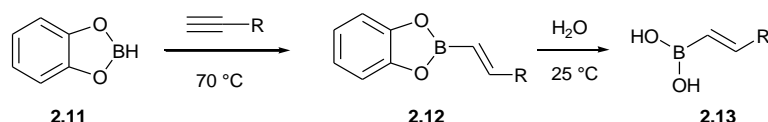
Scheme 2.2

2.3.3 Hydroboration

Transmetallation of lithium or Grignard reagents remains a standard procedure for the preparation of arylboron reagents.⁵ However, for the synthesis of alkenylboron compounds, limited access to these reagents and more recently the incompatibility with sensitive functionality, led to the discovery and preferential use of hydroboration methodology. Hydroboration involves addition of B–H compounds to unsaturated hydrocarbons and has become a traditional method for the synthesis of alkenylboron reagents.⁶ Early hydroboration reagents include, THF-borane⁷, 9-BBN^{8,9} and pyridine borane.¹⁰

Dialkoxyboranes are common hydroborating agents. For example, catecholborane (1,3,2-benzodioxaborole) **2.11** rapidly reacts upon heating with alkenes and alkynes to

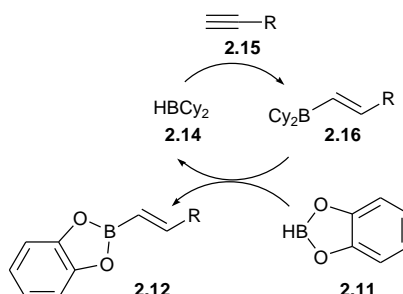
conveniently prepare alkyl and alkenylcatecholboranes (**2.12**) in high yields (Scheme 2.3).¹¹ Hydroboration is successful at 70 °C with neat reagents; terminal alkynes require only 1 hour, while internal alkynes require a slightly longer 2-4 hours. Specific *anti*-Markovnikov *cis*-addition occurs where the boron is attached regioselectively to the least hindered carbon of the triple bond.



Scheme 2.3

One drawback is that (*E*)-alkenylcatecholboronic esters such as **2.12**, once isolated by distillation, need to be stored under nitrogen. However, they can easily be hydrolysed to alkenylboronic acids *via* stirring in excess water at room temperature. The catechol by-product is water soluble whilst alkenylboronic acids are insoluble and hence conveniently isolated by filtration. Alternatively, they can be transesterified to more stable alkenylboronic esters.

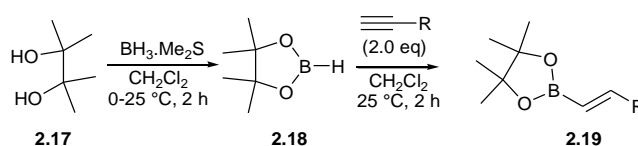
Over time, additives have been employed with catecholborane to enable milder conditions. For example, N,N-diethylaniline-borane complex and an excess of the alkyne enables the reaction to take place at room temperature in 24 hours.¹² Furthermore, addition of catalytic amounts of dicyclohexylborane (**2.14**) in THF at room temperature has also successfully yielded alkenylboronic esters.¹³ The mechanism proposed for the latter reaction is shown in Scheme 2.4. Hydroboration by dicyclohexylborane **2.14** is followed by hydride exchange with catecholborane **2.11** to regenerate dicyclohexylborane and form 1-alkenylboronic ester **2.13**.¹⁴



Scheme 2.4

Despite the success of this method, alkenylcatecholboronic esters and alkenylboronic acids are water sensitive, difficult to handle and purify. Therefore other 1,3,2-dioxaborolanes have also been used as hydroborating agents to generate more stable products.¹⁵

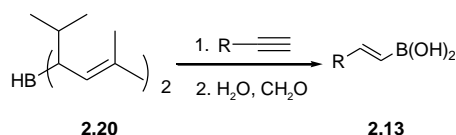
In more recent years, pinacol borane (4,4,5,5-tetramethyl-1,3,2-dioxaborolane) **2.18** has been utilised to achieve the more stable alkenylboronpinacolate esters **2.19** (Scheme 2.5). Pinacolborane, prepared by Knochel and co-workers in 1992,¹⁶ is considered an efficient hydroborating reagent. It is highly stable, functional group tolerant and requires mild reaction conditions, however reactions can be slow.¹⁷



Scheme 2.5

Hoshi and co-workers reported that dicyclohexylborane can also mediate hydroboration with pinacolborane under neat conditions at room temperature.¹⁴ They later determined this was also possible by bis(pentafluorophenyl)borane, $\text{HB}(\text{C}_6\text{F}_5)_2 \cdot \text{SMe}_2$.¹⁸ This came as no surprise as $\text{HB}(\text{C}_6\text{F}_5)_2$ hydroborates alkynes. However, it is a difficult reagent to synthesise and the alkenylboronate generated is unreactive and unstable.¹⁹ As such $\text{HB}(\text{C}_6\text{F}_5)_2 \cdot \text{SMe}_2$ is generated *in situ* and used catalytically with pinacolborane to transfer the 1-alkenyl group from boron to boron.

A more recent hydroboration procedure has been developed using a new organoborane, di(isopropylprenyl)borane **2.20**. The reagent is generated *in situ* and provides smooth, convenient access to alkyl and alkenylboronic acids under mild conditions (Scheme 2.6).²⁰



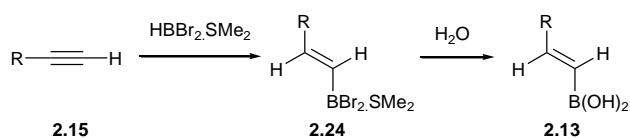
Scheme 2.6

Dichloroborane dioxane **2.22** is an easily synthesisable, inexpensive hydroborating reagent which gives the corresponding dichloroboranes (**2.23**) that are hydrolysed to the corresponding boronic acids (Scheme 2.7).²¹ The organoborane **2.22** is formed by reaction of borane or NaBH₄ with BCl₃ and 1,4-dioxane (**2.21**). It reacts stereo and regioselectively with highly selective *anti*-Markovnikov addition, with a range of terminal alkynes to generate (*E*)-alkenylboronic acids in modest to good yields.²²



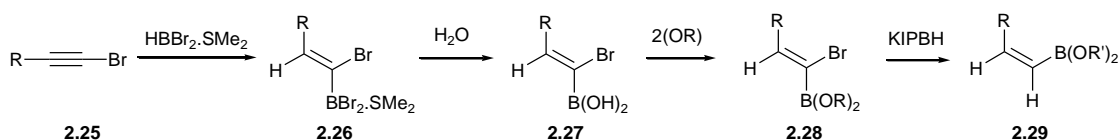
Scheme 2.7

Several methods which typically give (*E*)-alkenylboronates have been further developed with variations to also enable formation of (*Z*)-alkenes. A very popular hydroboration procedure utilises dibromoborane-dimethylsulfide (HBBr₂.SMe₂), which easily transforms alkynes into (*E*)-alkenylboronic acids *via* an (*E*)-alkenyl dibromoborane-dimethylsulphide complex **2.24** (Scheme 2.8).²³



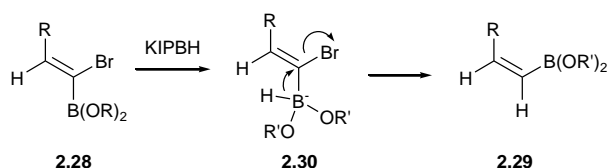
Scheme 2.8

HBBr₂.SMe₂ has also been utilised in the synthesis of (*Z*)-alkenylboronic esters **2.29** from 1-bromo-alkynes (**2.25**), as detailed in Scheme 2.9.²⁴ Hydroboration is followed by a hydrolysis-esterification procedure to generate (*Z*)-(1-bromo-1-alkenyl)boronic esters **2.28** which are subsequently transformed into (*Z*)-alkenylboronic esters **2.29** using potassium triisopropoxyborohydride (KIPBH) in ether at room temperature.



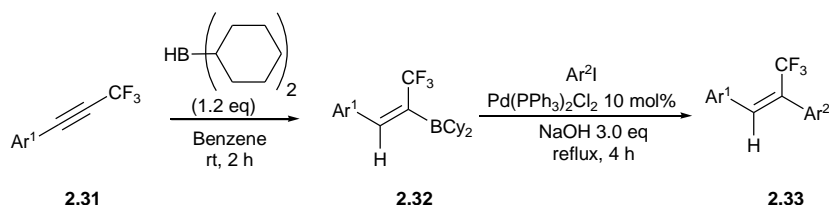
Scheme 2.9

KIPBH facilitates a hydride transfer to the boronic ester **2.28** to form species **2.30** (Scheme 2.10). This is followed by a hydride migration to the vinyl carbon to complete the transformation to the (*Z*)-alkenylboronic ester **2.29**.



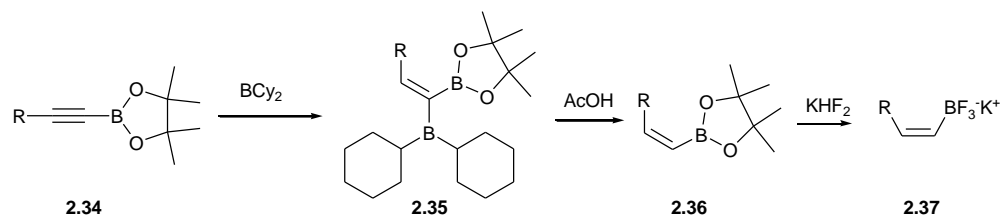
Scheme 2.10

Cy₂BH has been demonstrated as a mediator for less reactive hydroborating agents, but has also been used alone in one-pot syntheses, without isolation of the alkenylboron intermediates. In 2004, Konno *et al.* completed hydroboration of fluorine containing internal alkynes **2.31** followed by a Suzuki reaction to generate fluoroalkylated alkenes **2.33** (Scheme 2.11).²⁵ The hydroboration was determined as *cis* by protodeboronation of the alkenylboron to the *cis* alkene *via* hydrolysis. Upon reaction of the alkenylboron **2.32** with aryl iodides, under Suzuki-Miyaura conditions, (*Z*)-alkenes **2.33** were generated with high regio and stereoselectivity.



Scheme 2.11

Owing to the *anti*-Markovnikov selectivity of standard hydroboration methods, *cis*-alkenylboron compounds are often difficult to synthesise using these methods. An unusual synthesis of *cis*-alkenylboron reagents was reported by Molander and Ellis using a hydroboration and selective protodeboronation strategy.²⁶ It utilises the difference in reactivity between boronpinacolate esters and dialkylborons. Hydroboration of alkynylboronpinacolate **2.34** with dicyclohexylborane **2.14** generated 1,1-diboraalkenes *via cis* addition of the borane (Scheme 2.12). Subsequent chemoselective protodeboronation of the dicyclohexylboron group, using 1.0 eq of acetic acid at 0 °C, successfully gave *cis*-alkenylboronpinacolates **2.36**. Typically they transfer the ester to the trifluoroborate salt using standard methodology to complete the synthesis of *cis*-alkenyl trifluoroborate salts **2.37**.



Scheme 2.12

2.3.4 Catalytic methods: hydroboration, borylation, dehydrogenative hydroboration

Although traditional hydroboration methods are now common for large scale preparations, catalytic reactions are an interesting strategy for obtaining different chemo-, regio-, and stereoselectivities for alkenylboron reagents.

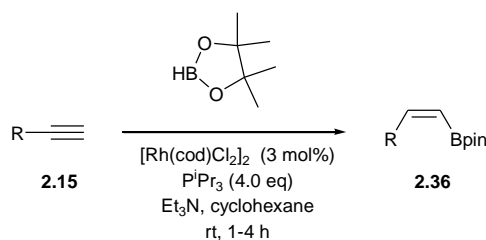
Modern methods include catalytic hydroboration which has also become common place and is particularly useful for *cis*, or more substituted alkenylboronates.⁶ Other catalysed methods include halogen-boron exchange, metathesis and dehydrogenative hydroboration. Many of these methods were developed with particular alkenylboron compounds in mind.

Catalytic hydroborations were first explored in 1985 using Wilkinson's complex $[\text{RhCl}(\text{PPh}_3)_3]$ to catalyse the addition of catecholborane to alkynes and alkenes at room temperature.²⁷ Since then it has been determined that catalytic hydroborations can accelerate existing hydroboration methodologies to afford standard *anti*-Markovnikov addition. A number of transition metals have been used as catalysts, but rhodium²⁸ has remained the most prevalent. Other transition metals employed in catalytic hydroborations include titanium,²⁹ palladium, ruthenium and zirconium.³⁰

A recent review by Song demonstrates pinacolborane as the most versatile hydroborating agent for many of these catalytic procedures.³¹ It offers many advantages over catecholborane; it requires milder conditions, gives better regio- and stereoselectivities and the boronpinacolate esters produced are stable to chromatography and water.

Pinacolborane usually furnishes (*E*)-1-alkenylboronic esters through *anti*-Markovnikov *syn*-addition to terminal alkynes. However, Miyaura and co-workers reported *trans*-hydroboration under Rh(I)- and Ir(I)- P^iPr_3 catalysis with Et_3N .³² The catalyst is

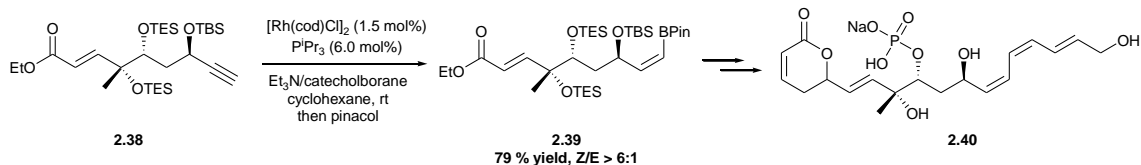
generated *in situ* from $[\text{Rh}(\text{cod})\text{Cl}]_2$ and P^iPr_3 and completes hydroboration at room temperature within 1 hour (Scheme 2.13).



Scheme 2.13

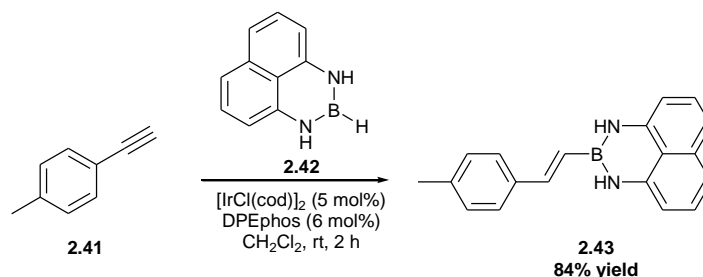
More than 1.0 eq. of Et_3N is essential to achieve high selectivity and high yields. The alkyne is required in excess of the borane in order to favour *trans*-hydroboration, which is also influenced by the steric and electronic effects of the ligand. Both pinacolborane and catecholborane afford (*Z*)-alkenylboronic esters under these conditions.

Recently Miyaura's conditions above have been used as a key step in the total synthesis towards fostriecin **2.40** (Scheme 2.14). (*Z*)-alkenylboronpinacolate **2.39** is constructed for use in a late stage Suzuki coupling.³³ Catecholborane is used, but the resulting boronic ester is transesterified with pinacol to construct (*Z*)-alkenylboronpinacolate **2.39** in a 6:1 ratio of *cis:trans*.



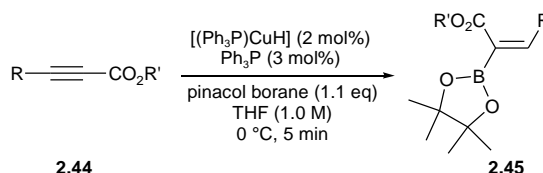
Scheme 2.14

In more recent years iridium catalysis has been employed. Iwadata and Suginome have described iridium catalysed hydroboration using 1,8-naphthalenediaminatoborane (HBDAN) **2.42** to synthesise DAN protected (*E*)-alkenylborons such as **2.43** (Scheme 2.15).³⁴



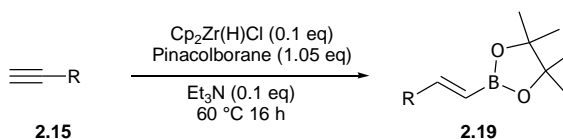
Scheme 2.15

An interesting procedure utilises copper hydride catalysis to perform *syn*-hydroboration of acetylenic esters **2.44** with pinacolborane (Scheme 2.16). 1,2-*Syn* hydrocupration occurs rapidly followed by transmetallation with pinacolborane with stereoretention.³⁵ A concentration of 1M or lower is necessary for successful reactivity and selectivity to generate (Z)-1-(alkoxycarbonyl)alkenylpinacolboronic esters **2.45** which have remarkable stability. The usefulness of this procedure and these compounds is their valuable α -carboalkoxy group.



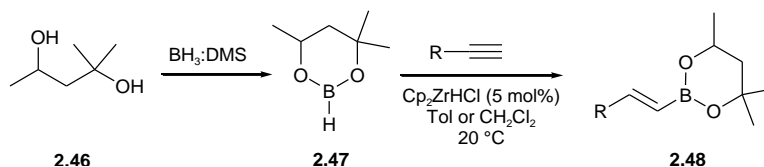
Scheme 2.16

Pereira and Srebnik reported that Schwartz reagent (Cp₂ZrHCl) catalyses hydroboration of terminal and internal alkynes with pinacolborane at room temperature with excellent *syn* selectivity.¹⁷ For less reactive alkynes, hydroboration can be slow and for oxygen containing alkynes, the selectivity for the (*E*)-alkenylboronic ester is poor. Thus the procedure has been modified by Wang and co-workers for more challenging alkynes (Scheme 2.17).³⁶



Scheme 2.17

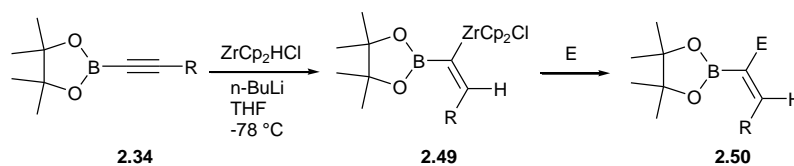
Chavant and co-workers have also described the use of Schwartz reagent with 4,4,6-trimethyl-1,3,2-dioxaborinane (methylpentanediolborane, MPBH) **2.46** to generate an alternative boronic ester to pinacol. MPBH has a facile synthesis as shown in Scheme 2.18. It hydroborates alkynes with Schwartz reagent at room temperature in either dichloromethane or toluene and proved more reactive than pinacolborane under these conditions.³⁷



Scheme 2.18

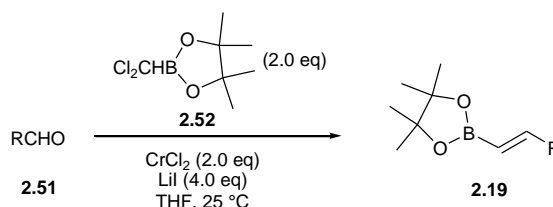
More recently Srebnik and co-workers have embellished their procedure by hydrozirconation of alkynylboronates **2.34** to obtain 1,1-borazirconocenes **2.49**. Upon

selective quenching with various electrophiles, for example aldehydes and ketones, highly substituted alkenylboronic esters **2.50** are formed (Scheme 2.19).³⁸



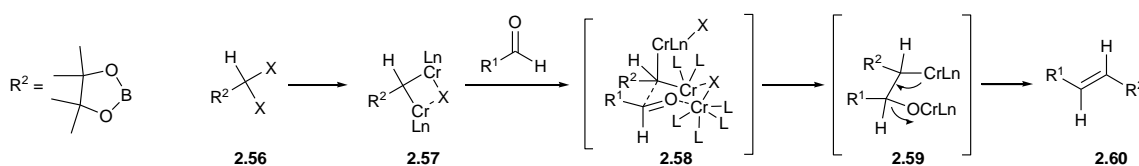
Scheme 2.19

Another methodology used to expand the functionality of the alkenylboronate is a dichromium catalysed transformation of aldehydes to (*E*)-alkenylboronic esters using dichloromethylboronic ester **2.52** (Scheme 2.20). Takai and co-workers demonstrate a high yielding and selective synthesis of a range of alkyl and aryl (*E*)-alkenylboronic esters.³⁹



Scheme 2.20

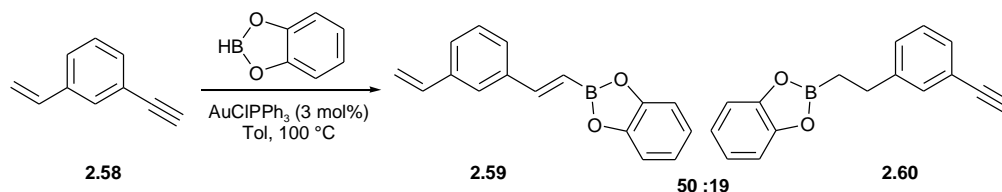
The high (*E*)-selectivity is explained by a pseudo chair transition state **2.58** of the reacted *gem*-dichromium species and the aldehyde; a halogen bridges two chromium ions and the R group substituents reside in the sterically favourable equatorial positions. Upon *syn*-elimination of $(\text{L}_n\text{Cr})_2\text{O}$ the (*E*)-olefin is generated. (Scheme 2.21)



Scheme 2.21

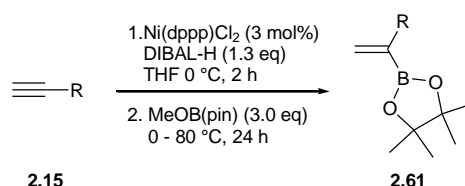
The reaction has since been successfully applied in the total synthesis of natural products 2'-O-methylmyxalamide D and (6*E*)-2'-O-methylmyxalamide D.⁴⁰

A gold catalyst has been demonstrated by Corm and co-workers as an alternative metal for catalysed hydroboration with remarkable chemoselectivity. Alkynes are hydroborated in preference to alkenes using either catecholborane or pinacolborane, (Scheme 2.22).⁴¹



Scheme 2.22

Also of significance is a recent nickel catalysed hydroboration which selectively synthesises internal alkenylboronpinacolate esters. Hoveyda and Gao report the synthesis of α -alkenylboronic esters **2.64** via hydroalumination using DIBAL-H and Ni(dppp)Cl₂ followed by reaction with methoxy(pinacolato)borane (Scheme 2.23).⁴²



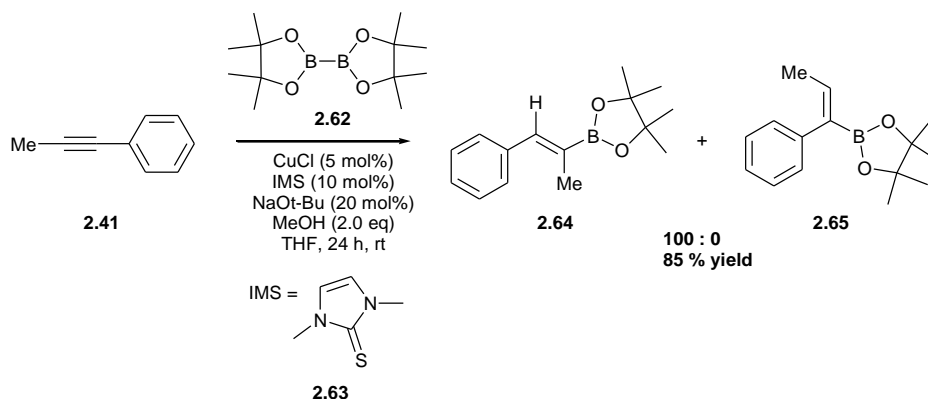
Scheme 2.23

The bidentate phosphine ligand is crucial to obtain the α -selectivity in excess of 98%. Replacement with a monodentate phosphine ligand such as triphenylphosphine reverses the selectivity to the typical β -adduct. N-heterocyclic ligands have been used with rhodium⁴³ and platinum⁴⁴ to also obtain internal boronates of this type, but not to the same level of selectivity.

Over the past decade, diboron reagents have become popular for enabling transition metal catalysed borylation. Similarly to borane reagents, these diborons have been used with a number of transition metal catalysts. It was initially reported with platinum by Miyaura and Suzuki in 1993,⁴⁵ then later using palladium, rhodium, iridium and copper.

Transition metal catalysed hydroboration of terminal alkynes with hydroboranes usually generates the *syn*-adduct which consequently forms (*E*)-alkenylboronates. However, regioselectivity issues can arise with internal alkynes. Hence, attempts at regioselective

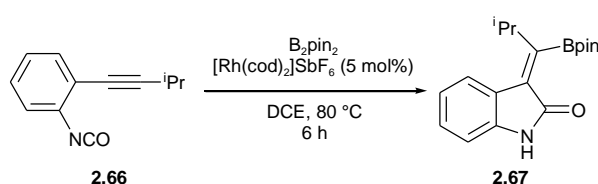
reactions with diboron reagents have been investigated. Recent conditions employ an imidazolidine-2-thione ligand **2.63** under copper catalysis with bis(pinacolato)diboron **2.62** to afford highly regioselective borylation of internal alkynes (Scheme 2.24).⁴⁶



Scheme 2.24

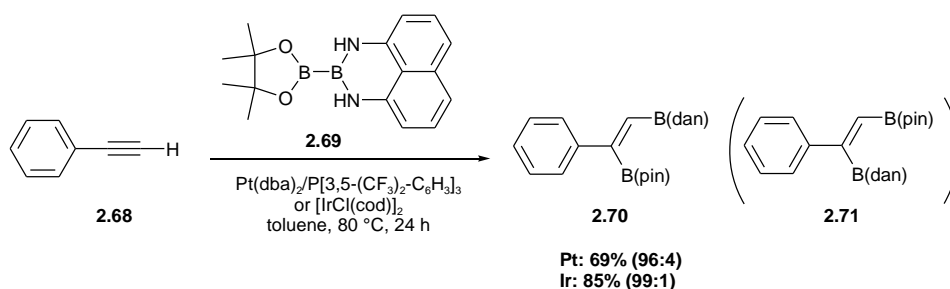
Under most conditions with alkynes, diboron reagents complete diboration in a *syn* fashion. Bis(pinacolato)diboron, B₂Pin₂, is the most commonly used diboron reagent, with platinum catalysis offering greater success than rhodium or palladium.^{47,48}

Recent applications have employed catalysed diborylation as part of tandem reactions to synthesise alkenylboronic esters. It is usually the external boronpinacolate that is reactive. For example, Scheme 2.25 shows borylated 3-alkylideneoxindoles such as **2.67** have been synthesised by rhodium catalysed borylative cyclization of 2-alkynylaryl isocyanates **2.66** with bis(pinacolato)diboron.⁴⁹



Scheme 2.25

Also possible is differentiated diborylation, using B(pin)B(dan) **2.69**, to diborylate terminal alkynes. The benefit of this is that the alkenylboronpinacolate can be cross coupled leaving a further protected alkenylboron which can be deprotected for further applications. Unlike symmetrical diboronalkenes, the reactive internal boronpinacolate undergoes cross coupling. Both Pt(dba)₂/[3,5-(CF₃)₂-C₆H₃]₃ and [IrCl(cod)]₂ gave the desired 1-alkenyl-1,2-diborons (**2.70:2.71**) in high yield and regioselectivity (Scheme 2.26).

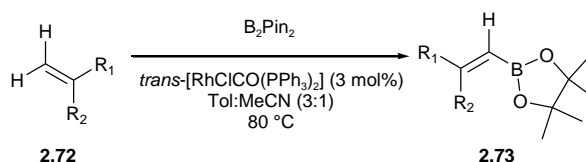


Scheme 2.26

Similarly to differentiated diboron species, other palladium catalysed di-additions are possible including silaboration⁵⁰ and cyanoboration.⁵¹

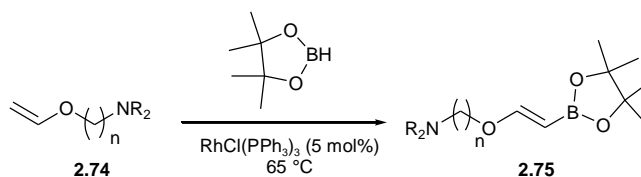
A further approach towards the synthesis of alkenylboron reagents is dehydrogenative-borylation. This is an effective alternative for C-B bond formation which is particularly useful for compounds which cannot be prepared by the hydroboration of alkynes. Dehydrogenative borylation involves C-H bond functionalisation of alkenes, thus the crucial requirement is for non hydrogenation and non hydroboration conditions, such that the alkene is borylated without consumption of the alkene. The use of diboron reagents can aid in preventing unwanted hydroboration pathways to give a more selective reaction.⁵² A number of transition metal catalysts have been utilised, most frequently rhodium, but also: iridium,⁵³ ruthenium,⁵⁴ platinum,⁵⁵ titanium⁵⁶ and iron.⁵⁷

Dehydrogenative borylation was pursued after it was seen as a side reaction under rhodium catalysed hydroboration conditions. Over the years there have been a number of reports utilising rhodium and investigating the ligands to continually improve the selectivity of dehydrogenative borylation over hydroboration and hydrogenation pathways.^{58,59,60,61} Marder and co-workers have demonstrated that *trans*-[RhCl(CO)(PPh₃)₂] is selective for dehydrogenative borylation of 1,1-alkenes **2.72** (Scheme 2.27).⁶²



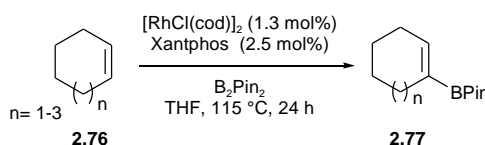
Scheme 2.27

Alternatively, Vogels and co-workers found $\text{Rh}(\text{Cl})(\text{PPh}_3)_3$ is highly selective in their dehydrogenative borylation of aminopropyl vinyl ethers (Scheme 2.28).⁶³



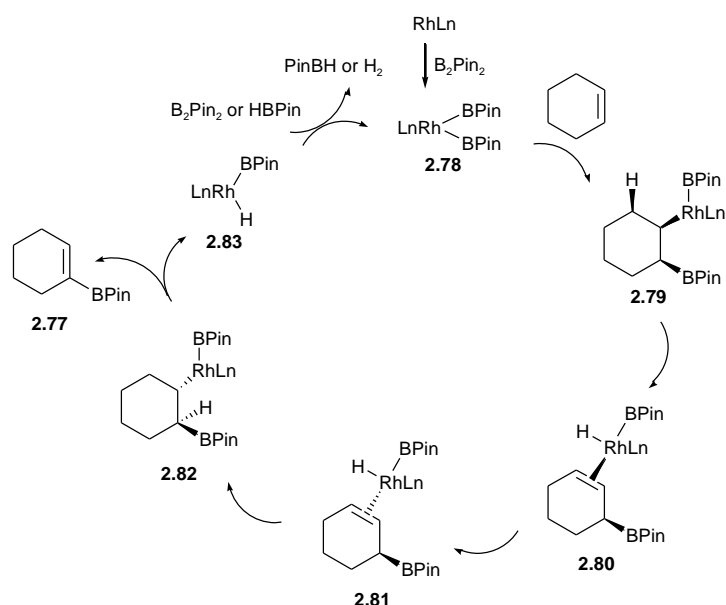
Scheme 2.28

An obvious advantage of catalytic dehydrogenative borylation over more classical approaches is for cyclic alkenylboronates since cyclic alkynes are unavailable. Kondoh and Jamison have recently reported an improved protocol for a more versatile C-H borylation of cyclic alkenes;⁶⁴ this rhodium-xantphos system depicted in Scheme 2.29 offers advantages over previous iridium^{65,66,67} catalysed methodologies. Only a slight excess of alkene is required and both boron atoms of the B_2Pin_2 reagent are utilised. The substrate scope is also wider than previously possible, tolerating 5 to 8 membered cyclic alkenes and norbornylene.



Scheme 2.29

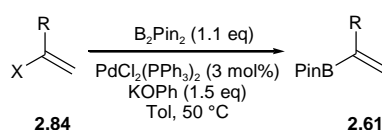
They propose an interesting mechanism (Scheme 2.30), whereby B_2Pin_2 undergoes oxidative addition to form a diboryl rhodium species **2.78**, followed by alkene insertion and β -elimination. Decomplexation at this point leads to the minor product they obtain, but in order to achieve the major isomer **2.77** an isomerisation must take place. This is likely to involve dissociation, re-complexation, hydrometalation and a β -hydride elimination. Alkenylboronpinacolate **2.77** is then formed along with a rhodium hydride species **2.83** which reacts with B_2pin or HBPIn to complete the catalytic cycle and regenerate the active rhodium-diboron complex. Thus, both borons of the B_2pin_2 are utilised.



Scheme 2.30

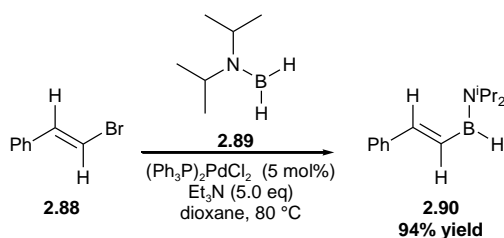
Another key route to alkenylboron reagents is the palladium catalysed borylation of alkenyl halides and triflates (Scheme 2.31). These mild reaction conditions have been extensively investigated for aryl iodides, bromides, chlorides and triflates.

1,1-alkenylboronates such as **2.61** in Scheme 2.31, are unavailable *via* classical hydroboration methodologies owing to unavailability of the alkynes and the *anti*-Markovnikov regioselectivity typically obtained. However, palladium catalysed borylation of corresponding acyclic and cyclic 1-alkenyl halides and triflates is a useful methodology for these otherwise challenging substrates.⁶⁸



Scheme 2.31

Common conditions for the borylation of cyclic vinyl triflates and iodides employ PdCl_2dppf with pinacolborane or bispinacolatodiboron.⁶⁹ Masuda and co-workers highlighted that under these conditions (*Z*)-alkenylhalides undergo complete inversion to (*E*)-alkenylboronates during the reaction.⁷⁰ More recently this was demonstrated by Alcaraz and co-workers in their palladium catalysed borylation of alkenyl halides with diisopropylaminoborane **2.89**, an alternative boron source to pinacol and catecholborane (Scheme 2.32).⁷¹

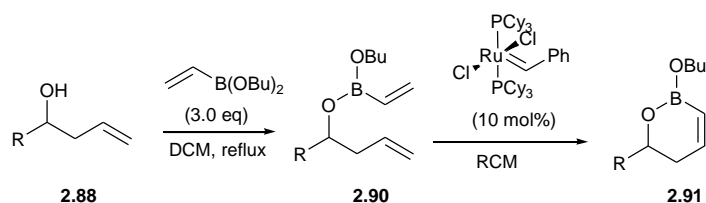


Scheme 2.32

Regardless of the starting stereochemistry of the styryl halide, only *trans*-styryl(diisopropylamino)boranes are formed.

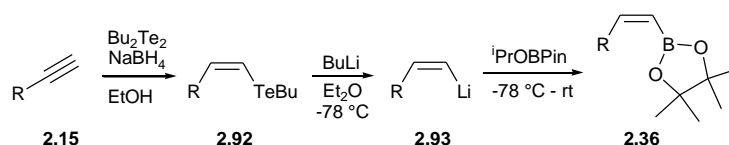
Aside from these main methods, examples of other strategies to synthesise alkenylboronates have been emerging. Cross-metathesis of vinylboronates and alkenes catalysed by ruthenium is a highly selective synthesis for *trans*-alkenylboronic esters and tolerates a wide range of functionality.⁷² The procedure has since been extended to synthesise more complex organoborons such as α -substituted alkenylboronates⁷³ and alkenylboron containing 1,3-dienes.⁷⁴

Most recently, metathesis has been applied in the synthesis of cyclic alkenylboronic half acids in which 1st generation Grubbs catalysts were most effective (Scheme 2.33).⁷⁵ The synthesis of these *cis*-substrates is likely to proceed *via* a subtly different mechanism. Alkenylborondibutyl ester **2.89** is the cross metathesis partner, which initially undergoes transesterification with homoallylic alcohols, followed by a ring closing metathesis to generate the *cis*-olefin **2.91**.



Scheme 2.33

Transmetallation of alkenyltellurides is also a recent method for the synthesis of *cis*-alkenylboron compounds (Scheme 2.34).⁷⁶ Hydrotelluration of alkynes proceeds in an *anti*-fashion and therefore selectively achieves *cis*-alkenyltellurides (**2.92**) which can be transmetallated to *cis*-alkenyl lithium **2.93** and quenched with isopropoxypinacolboronate. *cis*-Alkenylboronpinacolates (**2.36**) are achieved selectively with no isomerisation to the *trans* isomer.



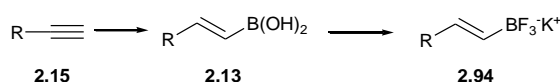
Scheme 2.34

2.4 Aims

To synthesise a number of alkynes and employ hydroboration strategies to prepare (*E*)-alkenyl trifluoroborate salts.

2.5 Synthesis of achiral potassium (*E*)-alkenyl trifluoroborate salts

For simple, unfunctionalised alkenylboronates, well established hydroboration methods are effective. Where possible, costs can be reduced by avoiding expensive metal catalysts when standard uncatalysed reactions are just as effective. Crucially, one drawback in many methods is the use of expensive diols. If it is possible to complete the synthesis of the trifluoroborate through the boronic acid, rather than an ester, the cost is lowered and atom economy improved. A number of alkynes are cheap and commercially available, therefore the desired alkenylboronates can be readily prepared from their corresponding alkynes by standard hydroboration procedures (Scheme 2.35).



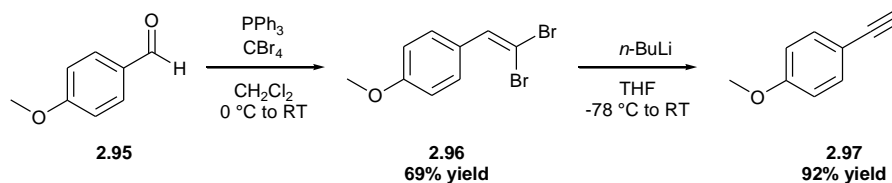
Scheme 2.35

However, the range of functionality of commercially available alkynes is somewhat limited. Therefore more functionalised alkynes were synthesised to extend the functionality of the alkenylboronates in order to expand our library of alkenylboronates for synthetic applications.

2.5.1 Synthesis of achiral alkynes

There are a variety of known procedures for the synthesis of alkynes.^{77,78,79,80,81,82} Aldehydes are cheap, commercially available, cover a range of functionality and have been applied in the Corey-Fuchs reaction to synthesise alkynes. This approach was used to synthesise 1-ethynyl-4-methoxy-benzene **2.97** from anisaldehyde **2.95** (Scheme

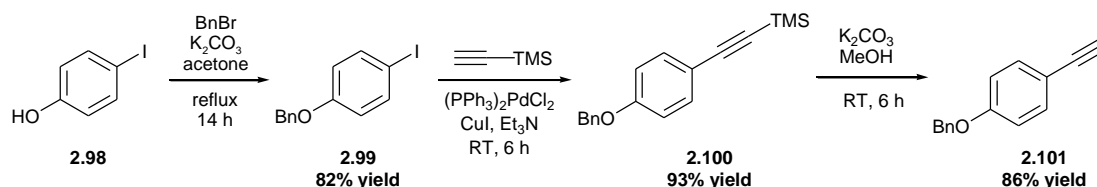
2.36). Initial reaction with carbon tetrabromide and triphenylphosphine afforded the dibromoalkene **2.96** in 69% yield. Subsequent treatment with *n*-butyllithium furnished the desired alkyne in 92% yield.



Scheme 2.36

Another approach to diversify the functionality was envisaged using commercially available alkynes such as trimethylsilylacetylene, homopropargylic and propargylic alcohols.

The first route utilises the Sonogashira reaction to couple trimethylsilylacetylene with arylhalides followed by trimethylsilyl deprotection to form the desired alkyne. This straightforward protocol worked successfully in high yields to synthesise 1-benzyloxy-4-ethynyl-benzene **2.101** as shown in Scheme 2.37. Initially 4-iodophenol (**2.98**) was benzyl protected under standard conditions. Exposure of **2.99** to palladium catalysed Sonogashira conditions followed by a basic deprotection step successfully afforded alkyne **2.101** in excellent yield.



Scheme 2.37

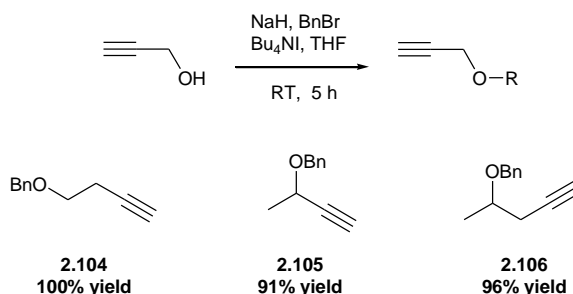
The second route to further expand alkyne functionality uses commercially available alcohol-containing alkynes. There is great potential for further functionalisation *via* standard procedures such as the Mitsunobu reaction, esterification and alcohol protection. With particular natural product precursors in mind, a number of propargylic and homopropargylic alcohols were protected using standard conditions.

As the yield for the benzyl protection of 4-iodophenol was only moderate, literature procedures were examined. As shown by the benzyl protection of propargyl alcohol **2.102** in Scheme 2.38, NaH with benzyl bromide improved the yield of the reaction at room temperature.



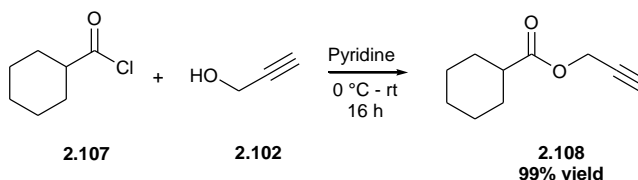
Scheme 2.38

The addition of a catalytic amount of Bu_4NI offered further improvements by *in situ* transformation of benzyl bromide into the more reactive benzyl iodide. Quantitative yields were reached in the shortened reaction time of 5 h at room temperature (Scheme 39).



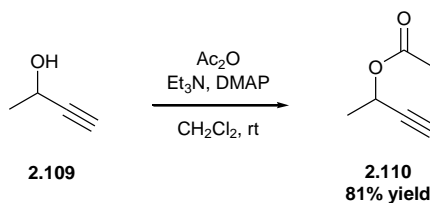
Scheme 39

Propargyl alcohol (2.102) was also esterified with benzoyl chloride 2.107 in pyridine to form alkyne 2.108 in 99% yield (Scheme 2.40).

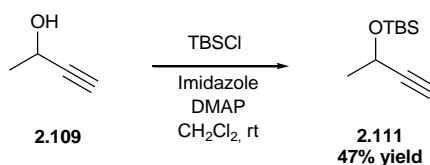


Scheme 2.40

But-3-yn-2-ol (2.109) was also protected by acetyl and TBS groups using standard procedures to afford alkynes 2.110 and 2.111 in 81% and 47% yield respectively.



Scheme 2.41



Scheme 2.43

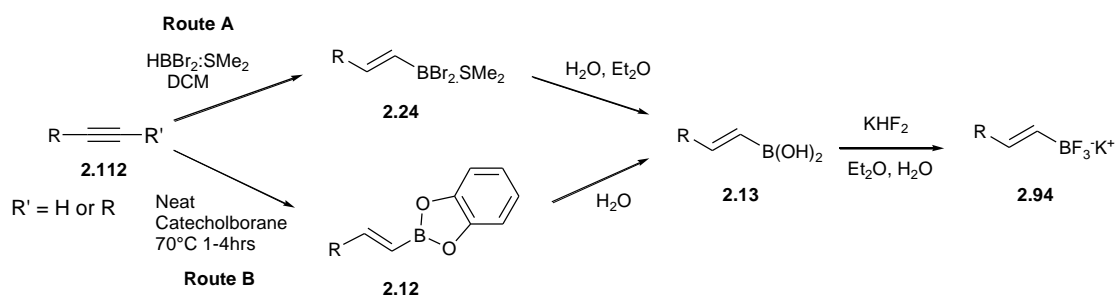
2.5.2 Hydroboration

As discussed there are a number of methods for synthesising alkenylboronates. Standard hydroboration methods were of interest in order to synthesise *trans*-alkenylboronates from our terminal alkynes. Two standard hydroboration procedures were initially employed (Scheme 2.43). Route A uses $\text{HBBBr}_2 \cdot \text{SMe}_2$ in DCM, followed by aqueous hydrolysis and work-up to afford alkenylboronic acid **2.13**. Route B requires more air sensitive conditions; refluxing the alkyne **2.112** in neat catecholborane under an inert atmosphere. On cooling and quenching with water again boronic acid **2.13** is formed. Standard procedures were subsequently followed to obtain the trifluoroborate salt **2.94** by reacting boronic acids with KHF_2 in Et_2O /water.

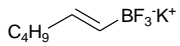
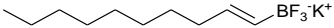
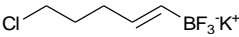
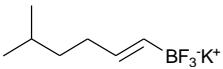
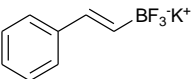
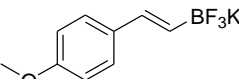
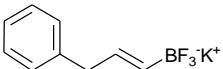
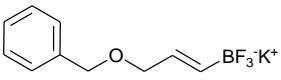
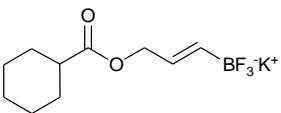
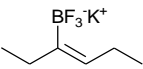
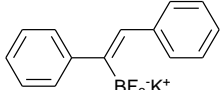
Alkenylboronic acids are known to be difficult to isolate and unstable in air, therefore in all cases they were taken directly, without isolation, to the potassium trifluoroborate salts which are air and moisture stable powders.

Commercially available alkynes, 1-hexyne, 1-decyne, phenylacetylene and 3-hexyne were exposed to route A to synthesise potassium alkenyl trifluoroborate salts **2.113**, **2.114**, **2.117** and **2.122** respectively (Table 2.1). Commercially available prop-2-ynyl-benzene and synthesised alkynes 1-ethynyl-4-methoxy-benzene **2.97** and cyclohexanecarboxylic acid prop-2-ynyl ester **2.108** were exposed to route B and afforded potassium alkenyl trifluoroborates **2.117**, **2.118** and **2.121**.

Commercially available alkynes 5-chloro-1-pentyne, 5-methyl-1-hexyne, diphenylacetylene and synthesised prop-2-ynyloxymethyl-benzene **2.103** were reacted under route A and route B to afford potassium alkenyl trifluoroborate salts **2.115**, **2.116**, **2.123** and **2.120** (Table 2.1).



Scheme 2.44

$\text{BF}_3 \cdot \text{K}^+$ salts	Compound No.	Method	% Yield (over 3 steps) ^(a)
	2.113	A	57
	2.114	A	45
	2.115	A B	54 20
	2.116	A B	51 47
	2.117	A	45
	2.118	B	21
	2.119	B	31
	2.120	A B	0 57
	2.121	B	18
	2.122	A	40
	2.123	A B	32 23

(a) *Trans: cis* ratios were >99:1 apart from 2.123; 71:29

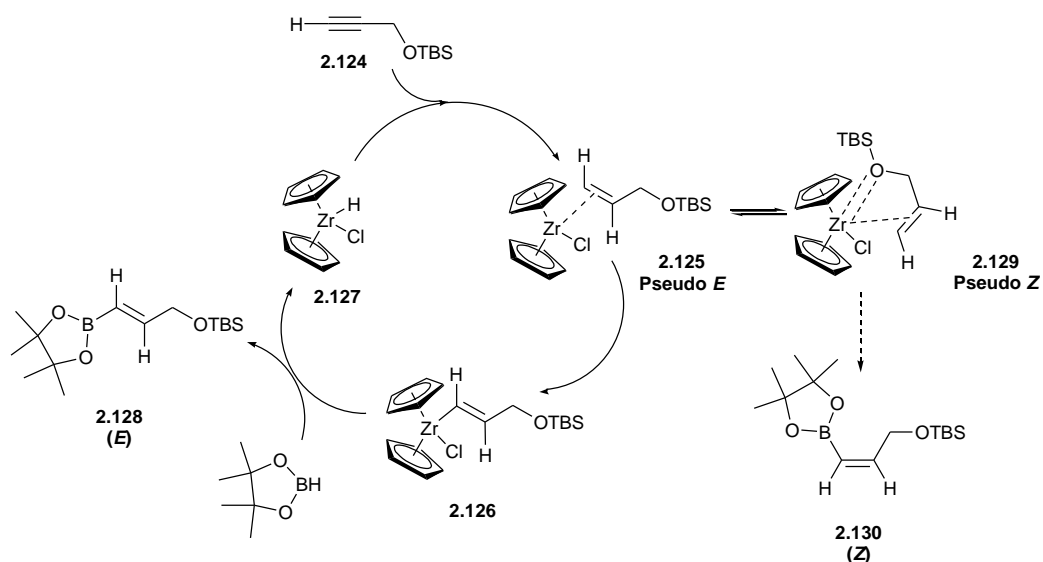
Table 2.1

Route B was more practically favorable owing to a 3-step-one-pot sequential procedure, where boronic acids suspended in solution could be transformed directly to the potassium trifluoroborate salt, without any need for work-up and exposure to air. In contrast, route A gave consistently good yields despite the required aqueous work-up. To avoid prolonged exposure to air and heat, the boronic acid was concentrated *in vacuo* at 20-30 °C, but not dried thoroughly.

Yields averaged at 39% over 3 steps which equates to about 73% yield for each step (Table 2.1). Interestingly, prop-2-ynyl oxymethyl-benzene **2.110** afforded the corresponding potassium alkenyl trifluoroborate salt in a very reasonable 57% yield over 3 steps using route B, however under route A no desired product was isolated. Cyclohexanecarboxylic acid prop-2-ynyl ester **2.108** afforded only 18% yield of the desired potassium alkenyl trifluoroborate salt. These inconsistent and low yielding results confirmed that other methods were required for more functionalised alkynes, especially those with pendent oxygen functionality.

Catalytic hydroboration methods offer more control over hydroboration, especially of functionalised alkynes. A very useful method for the hydroboration of oxygen-containing alkynes was reported by Wang and co-workers using Schwartz reagent (Cp_2ZrHCl). As shown in Scheme 2.17, this method desirably forms the (*E*)-alkenylboronic ester selectively in excellent yields for a number of oxygen-containing alkynes.

The mechanism proposed is outlined in Scheme 2.44. Previous methods using allylic or propargylic ethers have been less successful owing to an undesirable Zr-O interaction (**2.129**). Formation of a Zr-O bond would lead to the undesired (*Z*)-isomer (**2.130**) and prevent catalyst regeneration. The investigations by Wang and co-workers established that the Zr-O interaction could be prevented by heating the reaction to 60 °C and adding a catalytic amount of amine base, such as DMAP or triethylamine. Under these conditions the desired (*E*)-zirconiate intermediate (**2.126**) forms which is then trapped by pinacolborane to afford the (*E*)-pinacolboronate ester **2.128** in optimum yields and excellent selectivity.



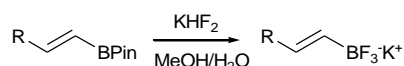
Scheme 2.44

Protected alkynes **2.101**, **2.103**, **2.104**, **2.105**, **2.106**, **2.110** and **2.111** were reacted with pinacolborane, catalytic Schwartz reagent and triethylamine in a flame dried Schlenk tube under an inert atmosphere. The reaction was refluxed whilst sealed from light to afford the corresponding (*E*)-alkenylboronpinacolate esters **2.131-2.137** in excellent yield and selectivities (Table 2.2). The conditions tolerated benzyl, acetyl and TBS protected alcohols.

$\text{R}-\text{C}\equiv\text{C}-\text{H} \xrightarrow[\text{Et}_3\text{N } 0.1 \text{ eq}, 60^\circ\text{C } 16 \text{ h}]{\text{Cp}_2\text{Zr}(\text{H})\text{Cl } 0.1 \text{ eq}, \text{Pinacolborane } 1.05 \text{ eq}}$			
Product	Compound No.	Yield	Selectivity (Z):(E)
	2.131	89%	>99:1
	2.132	98%	96:4
	2.133	95%	>99:1
	2.134	96%	97:3
	2.135	92%	99:1
	2.136	66%	94:6
	2.137	79%	99:1

Table 2.2

These pinacolate esters were easily transformed to the corresponding potassium alkenyl trifluoroborate salts **2.138** to **2.144** using the standard procedure (Table 2.3). The boron pinacolate esters were exposed to KHF_2 in $\text{MeOH}/\text{H}_2\text{O}$ at room temperature for 30 min and then concentrated. The residue was dissolved in acetone and filtered to remove the inorganic salts and excess reagent. It was therefore crucial to remove all water from the crude residue by trituration with Et_2O and high vacuum drying. The crude potassium trifluoroborate salts were easily purified by recrystallisation from hot acetone and Et_2O .



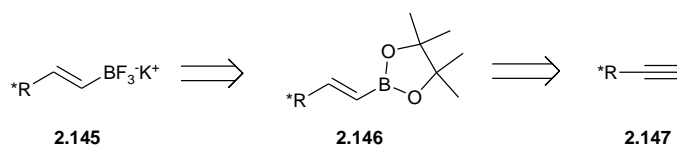
Product	Compound No.	Yield
	2.138	58%
	2.139	74%
	2.140	95%
	2.141	81%
	2.142	44%
	2.143	28%
	2.144	10%

Table 2.3

2.6 Synthesis of enantiopure potassium (*E*)-alkenyl trifluoroborates

For further synthetically useful purposes, in particular natural product synthesis, it would be highly desirable to access more functionalised, especially enantiopure alkenyl trifluoroborate salts. At the time, no enantiopure alkenylboronates had been reported. The rationale behind such an idea is that an enantiopure organoboron could be employed in a cross coupling reaction to install chirality and direct diastereoselectivity. The synthesis of enantiopure potassium alkenyl trifluoroborate salts can be considered

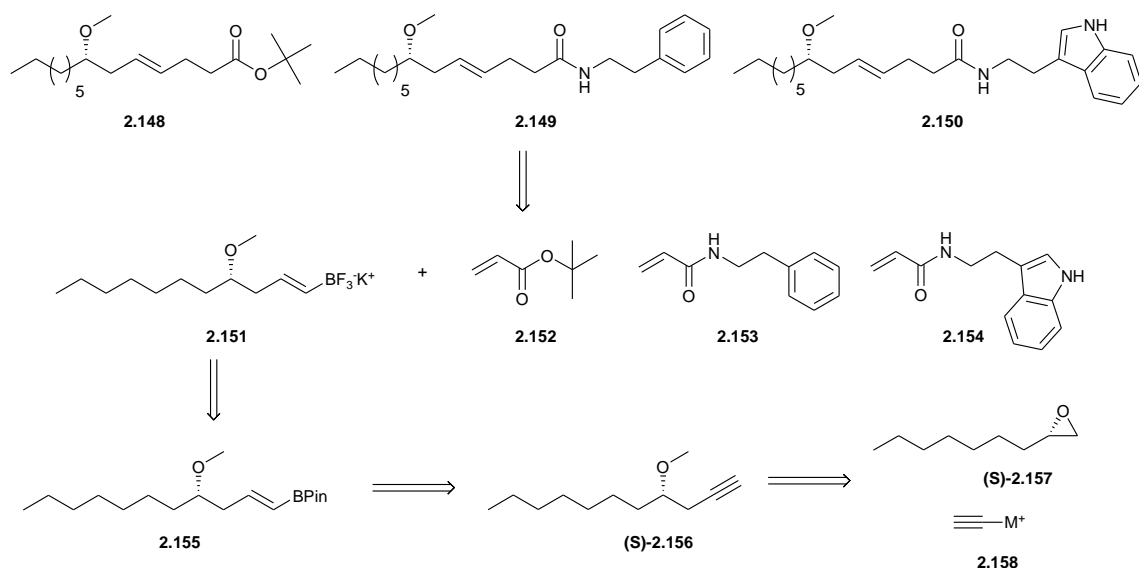
retrosynthetically as outlined in Scheme 2.45. Therefore access to enantiopure alkynes was the next challenge.



Scheme 2.45

2.6.1 Previous Work

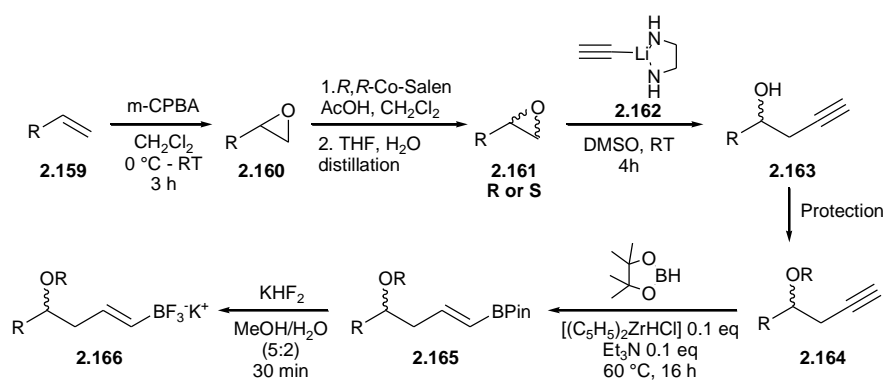
Previously within the group, natural products lyngbic acid and hermitamides A and B were of particular interest and their synthesis was envisioned through the rhodium catalysed conjugate addition of enantiopure alkenylboronate **2.151** to acceptors **2.152**, **2.153** and **2.154** (Scheme 2.46).



Scheme 2.46

The total synthesis towards these compounds was devised and successfully employed by previous group member Dr Penrose. Following the successful employment of zirconium catalysed hydroboration with achiral homopropargylic alcohols, it was plausible the method would also be successful with enantiopure alkynes such as **2.156** to afford alkenylboronate **2.155**. The enantiopure alkyne **2.156** was envisioned by ring opening of the relevant enantiopure epoxide.

After some investigation of different procedures by Dr Penrose, the finalised route was as described in Scheme 2.47.⁸³ The epoxide required for the natural product precursor was easily synthesised *via* standard epoxidation of 1-nonene **2.159** with meta-chloroperbenzoic acid (m-CPBA). Jacobsen's hydrolytic kinetic resolution is an efficient process for resolving epoxides to obtain enantiopure chiral epoxides and diols and as such was employed to access the enantiopure epoxide **2.161**. In order to form the homopropargylic alcohol **2.163**, nucleophilic ring opening of the epoxide was completed. Lithium acetylide complex with ethylene diamine (**2.162**) was considered most suitable for the large scale reaction and gratifyingly required short reaction times. The alcohol was methylated before the alkyne was reacted under Wang's zirconium catalysed hydroboration conditions, followed by KHF₂ to isolate the natural product precursor.



Scheme 2.47

Owing to the usefulness of the compound generated and our desire to create a library of novel potassium alkenyl trifluoroborates to apply synthetically, the generality of the route starting from enantiopure epoxides was explored.

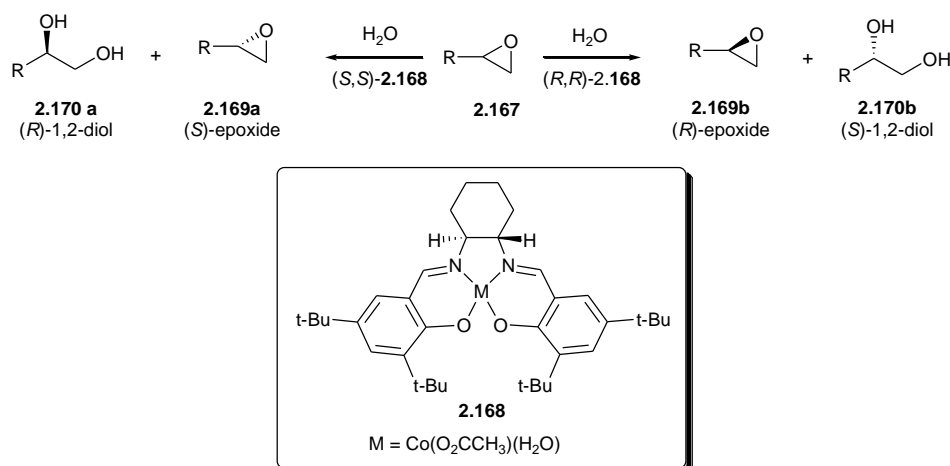
2.6.2 Aims:

To demonstrate the generality of methodology developed within the group to synthesise a number of novel enantiopure potassium alkenyl trifluoroborate salts.

2.6.3 Synthesis of enantiopure potassium (*E*)-alkenyl trifluoroborate salts

A number of epoxides are commercially available. Racemic epoxides, such as styrene oxide, are often cheaper than single enantiomers and can easily be kinetically resolved. Jacobsen and co-workers have demonstrated excellent conditions for the hydrolytic

kinetic resolution of epoxides which is one of the most widely used industrial scale asymmetric transformations (Scheme 2.48).^{84,85}

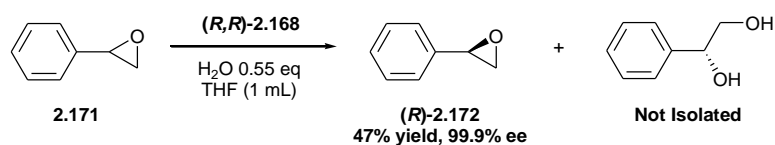


Scheme 2.48

The chemistry consistently forms highly enantiopure chiral epoxides **2.169a** and **2.169b** and 1,2-diols **2.170a** and **2.170b**, often exceeding 95% enantiomeric excess and achieving close to the maximum possible 50% yield. Both enantiomers of the chiral cobalt-salen complexes are widely available and inexpensive catalyst precursors.

In order to obtain a number of differentially protected alkynes a large quantity of enantiopure styrene epoxide was desired. Owing to the cost of each enantiomer on this scale, its preparation was envisioned following Jacobsen's first reported experimental procedure.⁸⁶

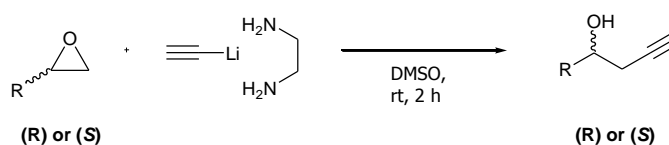
Commercially available N,N'-bis(salicylidene)ethylenediaminocobalt (II) was reacted with acetic acid in air for 1 hour to form the desired catalyst cobalt-salen ligand complex *in situ*. Following the removal of solvent, the dark brown solid residue was dissolved in neat epoxide and cooled to 0 °C for the dropwise addition of water. Minimal anhydrous THF was added to improve solubility thereby improving homogeneity. After stirring at ambient temperature for 72 hours the enantiopure epoxide **2.172** was isolated by distillation from the catalyst and diol at low vacuum (65 °C, 5 mmHg)⁸⁵ (Scheme 2.49).



Scheme 2.50

Enantiopure (*R*)-styrene oxide (**2.172**) was isolated as a colourless oil in 47% yield. Comparison with literature optical rotation and analysis of chiral HPLC confirmed the enantioselectivity was 99.9%.

With the desire to access examples with different alkyl chains, other epoxides were also required. As single gram scale quantities were needed, single enantiomers were purchased rather than synthesised. These included (*R*)-epichlorohydrin, (*S*)-2-oxiranylanisole, (*R*)-(-)-N-(2,3-epoxypropyl)phthalimide and *tert*-butyldimethylsilyl (*R*)-(-)-glycidyl ether. With enantiomerically pure epoxides in hand, nucleophilic ring opening was completed by lithium-acetylide, ethylene diamine complex in anhydrous DMSO. After stirring at room temperature for 2 hours an aqueous work up led to the desired enantiopure alkynes **2.173**, **2.174**, **2.175** and **2.176** which were of sufficient purity to be used directly without purification (Table 2.4).



Alkyne	Compound No.	Yield
	2.173	79%
	2.174	n.d
	2.175	85%
	2.176	30%

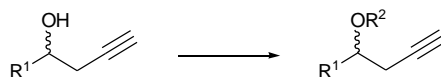
Table 2.4

(*R*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-pent-4-yn-2-ol **2.176** was isolated in a lower 30% yield. Epichlorohydrin yielded no desired product which could be accounted for by nucleophilic substitution of the chloride, or interaction with ethylene diamine.

The main concern with oxygen-containing alkynes is the affinity of boron for oxygen which has been reported by Li⁸⁷ to lead to elimination and generate an ene-yne. It is worth noting that an unprotected alcohol cannot undergo successful hydroboration and thus the alcohols required protection before hydroboration of the alkynes.

For our library of synthetically useful trifluoroborates a number of protecting groups would be useful, especially groups cleavable under different conditions. TBS and THP protecting groups had been reported by Wang and co-workers and Dr Penrose successfully demonstrated hydroboration of his propargylic methyl ether. Protecting with multiple groups has a two fold benefit in affording a range of novel compounds and to demonstrate the tolerance of a range of protecting groups under these hydroboration conditions.

(*R*)-1-Phenyl-but-3-yn-1-ol **2.173** was therefore protected with a range of protecting groups in good to excellent yield using standard literature conditions (Table 2.5, **2.177** to **2.182**). (*S*)-1-Phenoxy-pent-4-yn-2-ol **2.175** and (*R*)-1-(*tert*-butyl-dimethyl-silanyloxy)-pent-4-yn-2-ol **2.176** were successfully methylated to afford **2.183** and **2.184**.

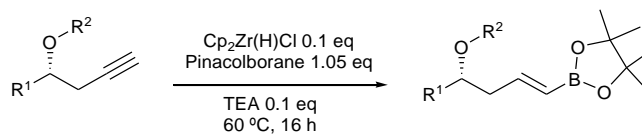


Alkyne	Compound No.	Yield
	2.177	67% ^(a)
	2.178	84% ^(b)
	2.179	77% ^(c)
	2.180	74% ^(c)
	2.181	86% ^(d)
	2.182	90% ^(e)
	2.183	74% ^(a)
	2.184	62% ^(a)

(a) (i)NaH (1.2 eq), THF 0 °C-75 °C 2 h, (ii) MeI (1.2 eq), 0 °C-75 °C 12 h; (b) NaH (1.0 eq), Bu₄NI (cat.), benzylbromide (0.8 eq), THF, rt; (c) Acylchloride (3.0 eq), Pyridine (8.0 eq), CH₂Cl₂; (d) Ac₂O (1.2 eq), Et₃N (1.4 eq), DMAP (0.5 eq), CH₂Cl₂; (e) TBSCl (1.2 eq), imidazole (1.2 eq), DMF

Table 2.5

Successfully protected alcohols were subsequently exposed to the zirconium catalytic hydroboration conditions. Pure (*E*)-alkenylboron pinacolate esters were isolated as yellow oils by passing the crude reaction mixture through a short silica plug, eluting with petroleum ether. Gratifyingly the desired (*E*)-alkenylboronic ester was isolated in all cases in excellent yield and stereoselectivity (Table 2.6).

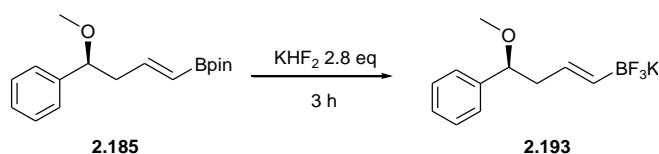


Boronic ester	Compound No.	Yield (%)	(<i>E</i>):(<i>Z</i>) ratio
	2.185	87%	99:1
	2.186	72%	96:4
	2.187	75%	88:12
	2.188	96%	91:9
	2.189	85%	86:14
	2.190	81%	92:8
	2.191	95%	96:4
	2.192	70%	89:11

Table 2.6

The boronic esters were relatively stable, but did begin to decompose on the bench top after several months. However, once transformed to the trifluoroborate salt they were stable indefinitely. Using standard procedures, boron pinacolate esters can be taken directly to potassium trifluoroborate salts which are easily isolated as white free flowing powders. As powders, the trifluoroborate salts demonstrate all the advantages reported previously about these reagents. They are easier to handle, more stable and should also display synthetic advantages in their reactivity.

The standard literature conditions contain moderate variations in time and solvent. Initially 2-(4-methoxy-4-phenyl-but-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane **2.185** was exposed to Molander's conditions using Et₂O/water and 2.8 eq KHF₂ and the corresponding trifluoroborate salt (**2.193**) was isolated in 56% yield. Working with multigram quantities and a number of examples this obviously required improvement to gain the most out of these novel reagents. A short screen of conditions revealed a potential reversibility or decomposition is taking place during the reaction. Acetonitrile⁸⁸ and methanol⁸⁹ have also been reported as appropriate solvents for the reaction and hence were also investigated (Table 2.7).



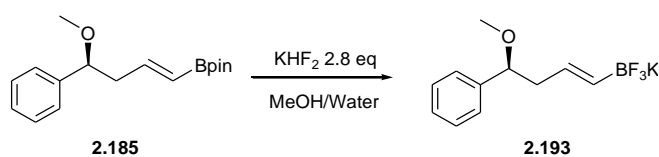
Entry	Solvent	Yield
1	Et ₂ O/water	56%
2	MeOH/water	58%
3	MeCN/water	43%

Table 2.7

Over 3 hours, acetonitrile had a detrimental effect, while methanol demonstrated a minimal improvement to 58% yield. This solvent effect could be owing to an improved solubility of the pinacolate ester combined with methanol/water miscibility creating a homogenous rather than two phase reaction medium which improves solubility of KHF₂. The potassium trifluoroborate salt is not soluble in Et₂O and sparingly soluble in methanol/water and therefore precipitates as it forms. Precipitation drives the reaction to product formation. Methanol would appear to be a convenient balance between these desirable properties. It was observed that in acetonitrile/water the trifluoroborate was

more soluble in the reaction mixture, with minimal precipitation as the reaction progressed.

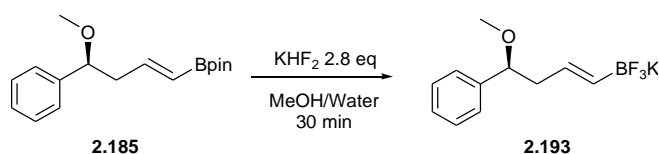
Most interesting was the effect of time upon the reaction (Table 2.8). Using the optimum solvent system methanol/water, the reaction was repeated over 0.5, 1 and 3 hours which clearly revealed decomposition of the product over the course of the reaction, either *via* protodeboronation or by reversibility of the reaction. The optimum time of 0.5 h afforded the desired potassium alkenyl trifluoroborate salt in 86% yield, but when left longer the yield decreased down to 58%.



Entry	Time (h)	Yield
1	0.5	86%
2	1	67%
4	3	58%

Table 2.8

Whilst 86% is very reasonable, it was proposed that with a greater excess of KHF_2 we could force the reaction towards product formation. Fortunately KHF_2 is inexpensive and indeed increasing the amount used to 9.0 eq afforded the desired product in 96% yield (Table 2.9).



Entry	KHF_2 eq.	Yield
1	2.8	86%
2	6	57%
3	9	96%
4	2.8 x 2	40%

Table 2.9

Crucial other factors to the reaction were the addition of KHF_2 in one portion followed by dropwise addition of water and evaporation of the reaction mixture under minimal water bath temperature (20-30 °C). The length of time required to satisfactorily remove water and pinacol on a large scale may well have contributed to only a short initial exposure time at room temperature. Trituration of the residue with small quantities of diethylether aided removal of water and pinacol as it was crucial the crude material was dried as far as possible in order to achieve successful recrystallisation in hot acetone/diethylether. Therefore MeOH/water (5:2), 9.0 eq. KHF_2 , for 0.5 h at room temperature became our optimal conditions for trifluoroborate formation from boron pinacolate esters.

Boron pinacolate esters **2.186** to **2.192** were successfully reacted under these conditions to afford suitable quantities of their corresponding potassium alkenyl trifluoroborate salts **2.194** to **2.200** in good to excellent yields (Table 2.10)

Low yields were obtained for products **2.194**, **2.196**, **2.198** and **2.200**, this could be owing to the speed of decomposition and hence the optimum reaction time needed probably varies between examples. In the case of TBS analogues **2.198** and **2.200**, the low yield could be accounted for by the deprotection of TBS by excess fluorinating agent KHF_2 . **2.198** was isolated as the deprotected alcohol which rendered the material more difficult to isolate. Also, the free hydroxyl could have co-ordinated to the boron and more facile protodeboronation taken place in the aqueous reaction mixture.

$ \begin{array}{ccc} \begin{array}{c} \text{R}^2 \\ \\ \text{O} \\ \\ \text{R}^1-\text{CH}-\text{CH}=\text{CH}-\text{Bpin} \end{array} & \xrightarrow[\text{MeOH/Water, 0.5 h}]{\text{KHF}_2 \text{ 2.8 eq}} & \begin{array}{c} \text{R}^2 \\ \\ \text{O} \\ \\ \text{R}^1-\text{CH}-\text{CH}=\text{CH}-\text{BF}_3\text{K} \end{array} \end{array} $		
Potassium trifluoroborate	Compound No.	Yield
	2.193	96%
	2.194	41%
	2.195	86%
	2.196	38%
	2.197	68%
	2.198	16%
	2.199	71%
	2.200	25%

Table 2.10

In essence a high yielding route was followed to generate a series of the first novel enantiopure potassium (*E*)-alkenyl trifluoroborate salts.

2.7 Synthesis of novel silyl-protected alkenyldioxaborinanes

In recent work within the group a new boron protecting group emerged (Figure 2.1).⁹⁰ These aryl borinanes were found to have increased reactivity as organoboron reagents under anhydrous conditions.

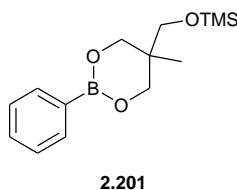
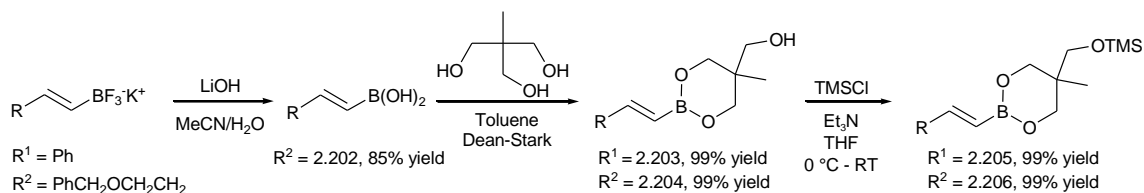


Figure 2.1

Therefore, two alkenyldioxaborinanes were prepared as detailed in Scheme 2.50. Conveniently styrylboronic acid is commercially available, however trifluoroborate **2.140** had been prepared and therefore required deprotection using standard literature conditions to achieve boronic acid **2.202**. In order to obtain quantitative yields for the esterification with 2-hydroxymethyl-2-methyl-propane-1,3-diol, boronic acid and triol were refluxed in toluene under dean-stark conditions. The pendant hydroxyl was the subjected to a TMS protection under standard conditions to afford dioxaborinanes **2.205** and **2.206** in 99% and 99% yield respectively.



Scheme 2.51

These novel compounds are yet to be extensively investigated, but it is likely they would demonstrate similar advantages to their aryl counterparts in synthetic reactions and be highly reactive alkenylboronic esters.

Their facile synthesis occurs in excellent yields and they are interconvertible with trifluoroborate salts. Whilst aryl derivatives form very stable free flowing powders, alkenyl derivatives are also solids, but have decreased long term stability in air.

2.8 Conclusions

Alkenyl boron reagents are readily synthesised *via* hydroboration of alkynes. A range of achiral alkynes were synthesised using established synthetic methodology. Two standard traditional hydroboration methods have been utilised to transform the alkynes into potassium (*E*)-alkenyl trifluoroborate salts.

The first family of enantiopure (*E*)-alkenyl potassium trifluoroborates have been synthesised. Their synthetic route has been discussed in detail, starting from epoxides to access a number of protected enantiopure homo propargylic alkynes. This work highlighted the benefit of advances in transition metal catalysed hydroboration methods for more functionalised substrates. In particular, the use of zirconium catalysed hydroboration is effective for oxygen containing alkynes. Fluorinating conditions were found to be reversible and hence were modified to improve the yields for transformation of the (*E*)-alkenylboronpinacolate esters to their corresponding trifluoroborate salts.

The first examples of alkenylborinanes have been synthesised using facile methodology. These novel reagents are alkenyl derivatives for this recently determined boron protecting group.

Essentially, a library of (*E*)-alkenylboronates has been obtained, they are highly functionalised, synthetically relevant and natural product precursors. As such, they are expected to be highly applicable donors in transition metal catalysed reactions in particular rhodium catalysed conjugate addition.

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Chapter 3: Rhodium catalysed additions of potassium alkenyl trifluoroborate salts

3.1 Overview: Alkenylorganoboron compounds are excellent donors for rhodium catalysed conjugate addition to α,β -unsaturated compounds. However, they are less widely accessible than corresponding arylorganoboron reagents and there are only a handful of examples of their application in rhodium catalysed conjugate additions. Problems such as protodeboronation still remain a major hindrance. Also the issue of alkene isomerisation when using alkenylboronates has not been addressed or its potential utilised.

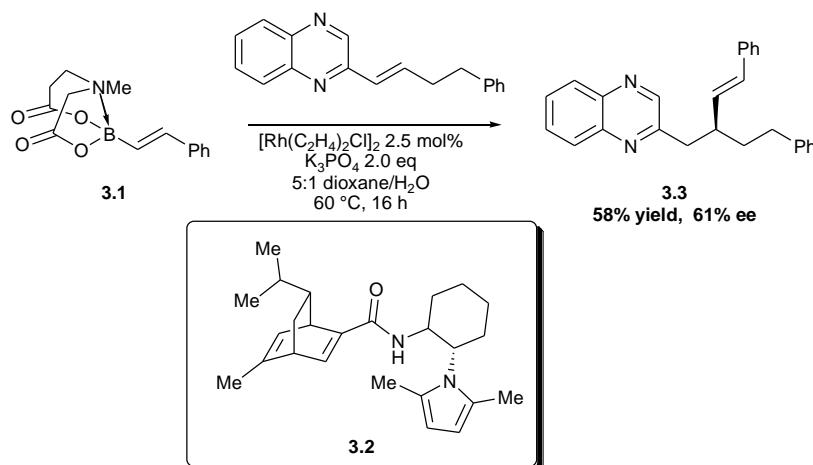
3.2 Aims: To apply potassium alkenyl trifluoroborates in the rhodium catalysed conjugate addition reaction to study and address issues concerning protodeboronation and isomerisation.

3.3 Synthetic applications of alkenyl boronates in the rhodium catalysed conjugate addition reaction

Chapter one discussed recent advances in the rhodium catalysed conjugate addition of arylboronates. Many of the modifications and features remain relevant and transferable to conjugate additions with alkenylboronates. Three sub classes of enantioselective conjugate addition were discussed and are equally applicable to alkenylboronates; prochiral substrates, enantioselective protonation and enantiopure acceptors. In addition, a further sub class of asymmetric conjugate addition is also made possible through the use of enantiopure organoboron donors.

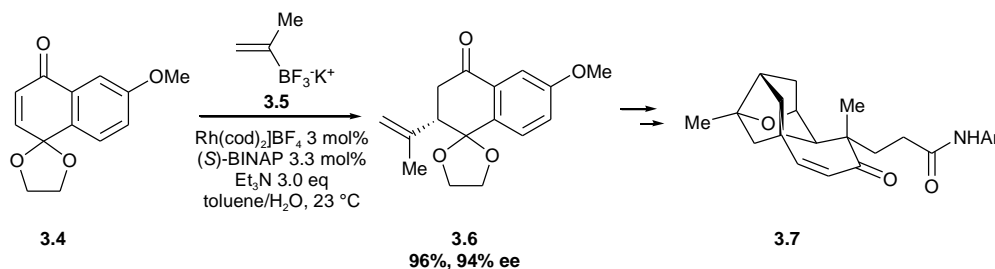
3.3.1 Prochiral acceptors

In a report by Lam and co-workers, the addition of alkenylboronic acids to more challenging, less reactive substrates such as alkenylheteroarenes proved largely unsuccessful and protodeboronation was isolated as the major product.¹ Their solution was in utilising styryl N-methyliminodiacetic acid (MIDA) boronate **3.1** to slowly release boronic acid *in situ*. The desired product was achieved in modest yield and enantioselectivity (Scheme 3.1).



Scheme 3.1

Corey and Lalic have employed secondary alkenyl trifluoroborates in enantioselective rhodium catalysed conjugate additions. Potassium isopropenyltrifluoroborate **3.5** was successfully added to enone **3.4** in high yield and enantioselectivity towards the formal total synthesis of platensimycin **3.7** (Scheme 3.2).² Optimised conditions employed (*S*)-BINAP in toluene at room temperature. Triethylamine was required to form an active rhodium-triethylamine complex to facilitate a room temperature reaction. This species is more electrophilic than the typical Rh-OH species and Et_3N is a more readily displaceable ligand, therefore boron-rhodium transmetalation is accelerated and Lewis-acid induced hydrolysis inhibited.

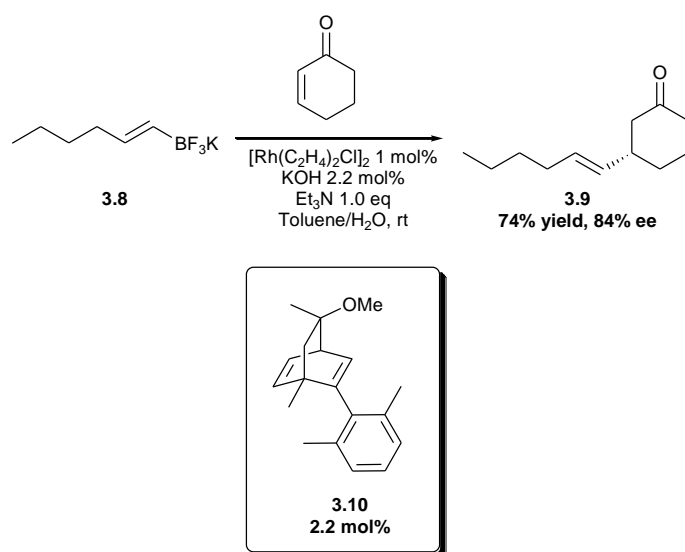


Scheme 3.2

Interestingly, at high temperatures some isomerisation was observed to the linear conjugate addition product. At 110 °C a 1:1 mixture of these isomers was obtained, however at room temperature no isomerisation occurred.

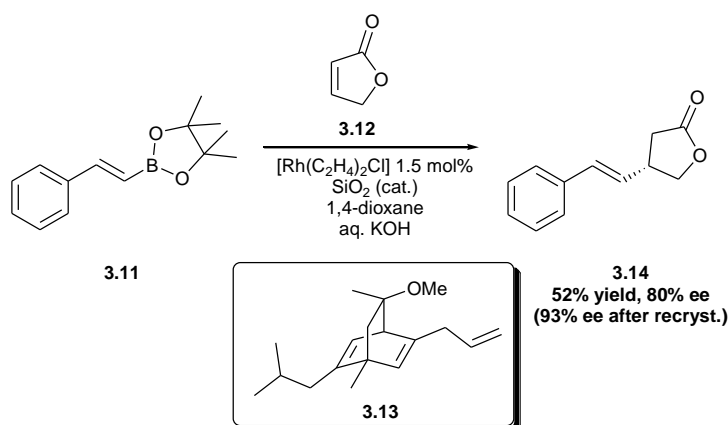
Similarly, Darses and co-workers have also utilised Et_3N to facilitate room temperature, enantioselective conjugate additions of potassium alkenyl trifluoroborate salts to α,β -unsaturated substrates.³ Good yields and enantioselectivities are obtained by employing enantiopure diene ligand **3.10** and 1.0 eq Et_3N (Scheme 3.3). For these substrates,

phosphine and phosphoramidite ligands were low yielding and gave low enantioselectivities.



Scheme 3.3

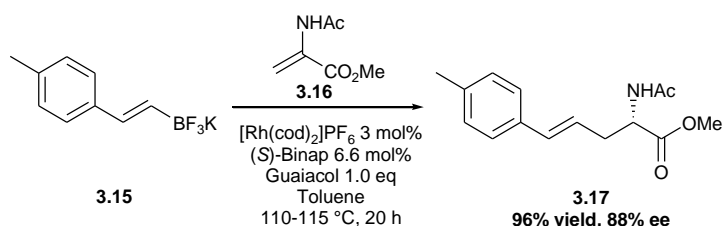
The rhodium catalysed conjugate addition of styryl boronpinacolate ester **3.11** to butenolide **3.12** was the initial step in the total synthesis of ecklonialactones (Scheme 3.4).⁴ Following Hayashi's conditions⁵ and employing Carreira's diene derived ligand (-)-carvone,⁶ the addition was completed in a modest 52% yield and 80% ee. Recrystallisation amplified the ee to 93%. Interestingly, they mention in a footnote, that while using (*S*)-BINAP, which required heating to 80 °C, the product was achieved in 73% ee, but partial isomerisation of the double bond also occurred. However, no precise detail, or yield of the isomerised compound is mentioned.



Scheme 3.4

3.3.2 Enantioselective protonation

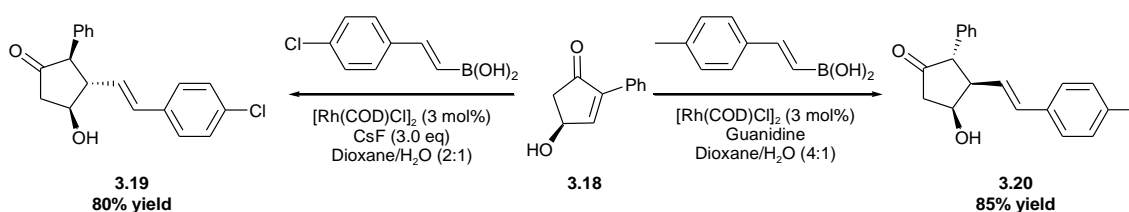
Gênet and Darses applied potassium alkenyl trifluoroborate **3.15** in a rhodium catalysed 1,4-addition/protonation to dehydroamino ester **3.16** (Scheme 3.5).⁷ The optimised conditions that achieved highest enantioselectivities with aryltrifluoroborates employed guaiacol as the proton source and (*S*)-BINAP as the chiral ligand. Cationic rhodium complexes were the most suitable catalyst precursors. High temperatures and non-polar solvents were also crucial for a successful reaction. In the application of potassium alkenyl trifluoroborate **3.15** under these conditions, the product was isolated as an inseparable mixture of conjugate addition **3.17** and 30% of the 3,4-isomer.



Scheme 3.5

3.3.3 Enantiopure acceptors

4-hydroxycyclopentenones **3.18** are useful precursors of prostaglandins. They have been employed in rhodium catalysed conjugate additions with aryl and alkenyl boronic acids, without protection of the hydroxyl moiety.⁸ Csáky and co-workers demonstrated additives could tune the stereochemical outcome of the reaction when using alkenylboronic acids (Scheme 3.6).



Scheme 3.6

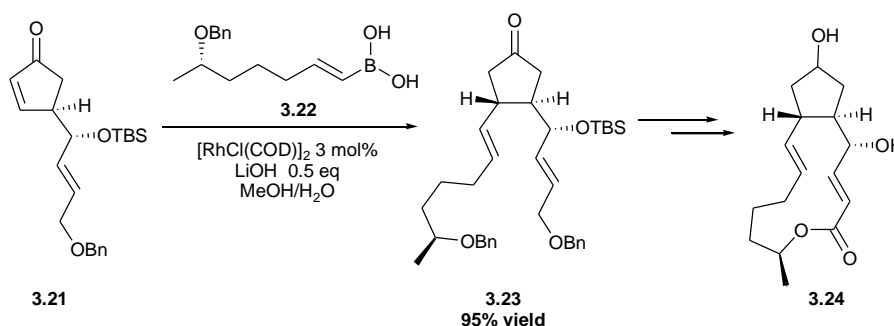
Being less bulky than aryl boronic acids, steric factors alone are not enough to control the stereoselectivity of the reaction towards the usual *trans* diastereomer **3.19**. The free hydroxyl coordinates to the rhodium complex directing the addition to the *syn* product **3.20** by using bulky guanidine as base. The *trans* product **3.19** can be accessed by

replacing base with CsF to disfavour the complexation, either by reducing basicity, or *via* formation of a saturated anionic rhodium complex $[\text{Rh}(\text{cod})\text{FRL}]^-$.

3.3.4 Enantiopure donors

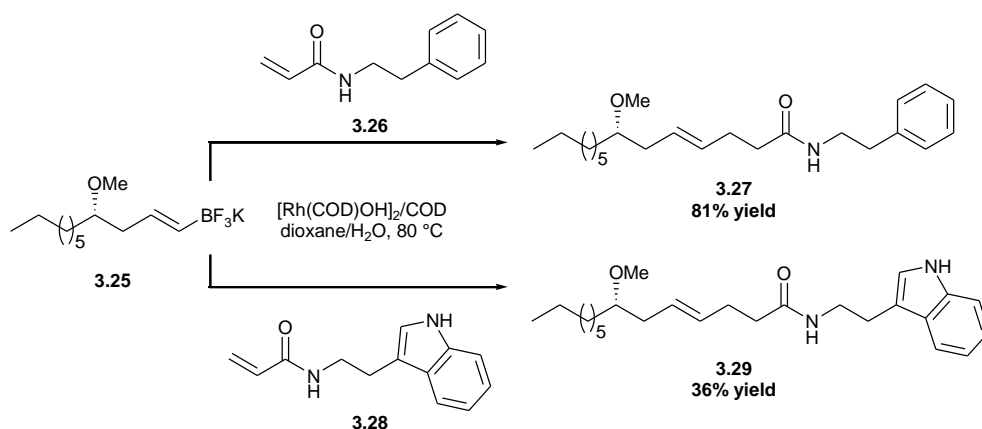
Enantiopure organoboron reagents have recently been applied in the rhodium catalysed conjugate addition reaction. Their application provides new synthetic strategies and access to unique intermediates.

For example, the rhodium catalysed conjugate addition of alkenylboronic acid **3.22** has been used as a key step towards an improved synthesis of brefeldin A **3.24** (Scheme 3.7).⁹ In many previous convergent syntheses, the lower side chain has been added to enone **3.21** *via* a Michael addition of an organolithium cuprate. Two equivalents of the *in situ* formed organometallic reagent are required and the reaction can be capricious. Fortunately, the rhodium catalysed addition is a simpler and more efficient process that is less sensitive to air and moisture. Impressively, a high yield was afforded using only a small excess (1.18 equivalents) of enantiopure organoboronic acid.



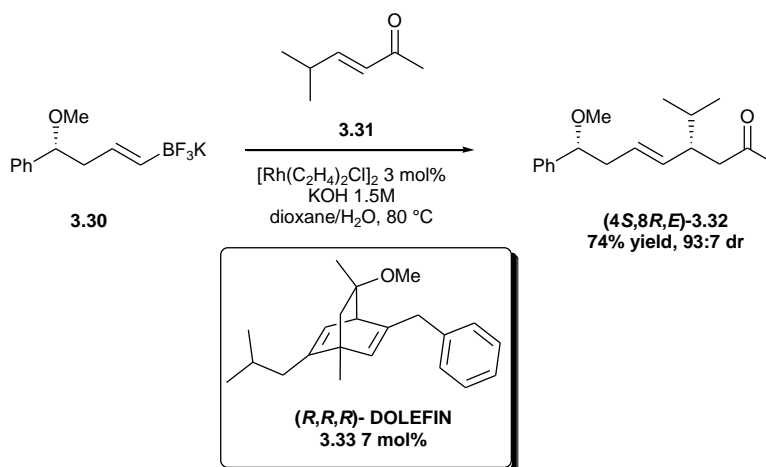
Scheme 3.7

Rhodium catalysed conjugate addition has also been a key step in the synthesis of hermitamides A and B.¹⁰ Scheme 3.8 highlights the route to both natural products *via* addition of an enantiopure alkenylboron reagent **3.25** to an acrylamide, employing $[\text{Rh}(\text{OH})(\text{COD})]_2$ as catalyst. The corresponding alkenylpinacolboronic ester afforded low yields and alkene-side products when reacted with acrylamide **3.26**. Fortunately potassium alkenyl trifluoroborate **3.25** reacted successfully without loss of stereochemical integrity and hermitamide A **3.27** was isolated in good yield. Similarly, hermitamide B **3.29** was also achieved by using tryptamine acrylamide derivative **3.28**.



Scheme 3.8

Frost and co-workers also investigated the addition of the enantiopure potassium alkenyl trifluoroborate **3.30** to acyclic enones such as **3.31** (Scheme 3.9).¹⁰ Excellent yields and diastereoselectivities were attained by employing Carreira's chiral bicycle[2.2.2]octadiene (DOLEFIN) ligand **3.33** and 1.5 M potassium hydroxide. The (*R,R,R*)-ligand provided (*4S,8R,E*)-diastereomer while (*S,S,S*)-ligand gave the complementary (*4R,8R,E*)-diastereomer.



Scheme 3.9

3.35 Conclusions

Alkenylorganoboron reagents can be reacted successfully under rhodium catalysed conjugate addition conditions. Once again, diene ligands often prove superior to phosphine ligands in achieving high enantioselectivities. Stereoselectivities can also be controlled through the use of enantiopure acceptors and donors. In a number of examples, frequently when employing phosphine ligands such as BINAP at high temperatures, isomerisation of the olefin has been observed.

3.4 Gas Chromatography studies of the rhodium catalysed conjugate addition reaction

3.4.1 Introduction

Protodeboronation has been a reported problem for some aryl and many alkenyl organoboron compounds. Upon initial application of many of our functionalised alkenyl trifluoroborate salts, it quickly emerged protodeboronation was a major problem and occurring in significant quantities.

There is much speculation, but little evidence in the literature about protodeboronation in transition metal catalysed reactions. Its occurrence as a side reaction has been used to account for the need for excess boron reagents and low yields. However, little is known about how protodeboronation occurs and there are conflicting views on whether or not it is a metal mediated process. Some reports have been made on additives and solvents decreasing protodeboronation as a result of seeing increased yields. However, no thorough investigation on what affects the rate of protodeboronation compared to the desired conjugate addition reaction of potassium alkenyl trifluoroborate salts has been reported.

3.4.2 Aims

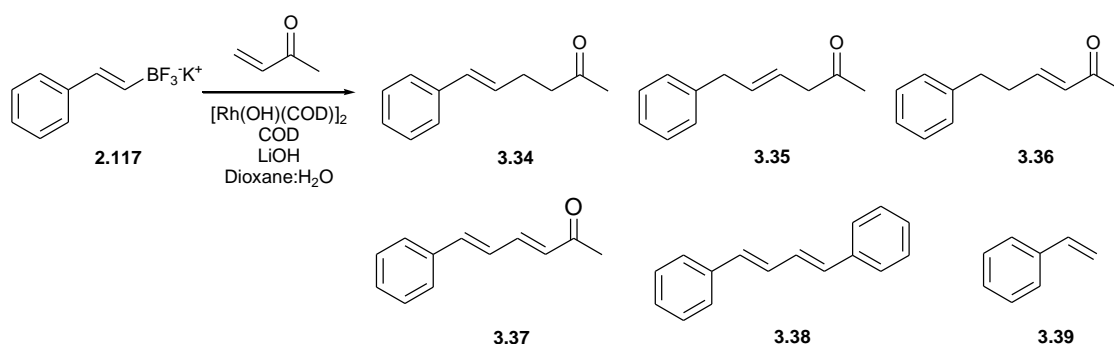
To use gas chromatography to follow the rhodium catalysed conjugate addition of potassium styryltrifluoroborate to MVK and determine conditions and additives that affect competing pathways, in particular protodeboronation.

3.4.3 Initial studies

In initial conjugate addition reactions, potassium styryltrifluoroborate was a problematic reagent. It formed mixtures of products with high yields of protodeboronated material and low yields of desired product. A number of the more functionalised trifluoroborates displayed similar problems, but since potassium styryltrifluoroborate is comparatively inexpensive and commercially available, it was chosen for the study. However, it does have a greater propensity towards homocoupling¹¹ compared to other organotrifluoroborates. Whilst results may not be exactly comparable, general trends

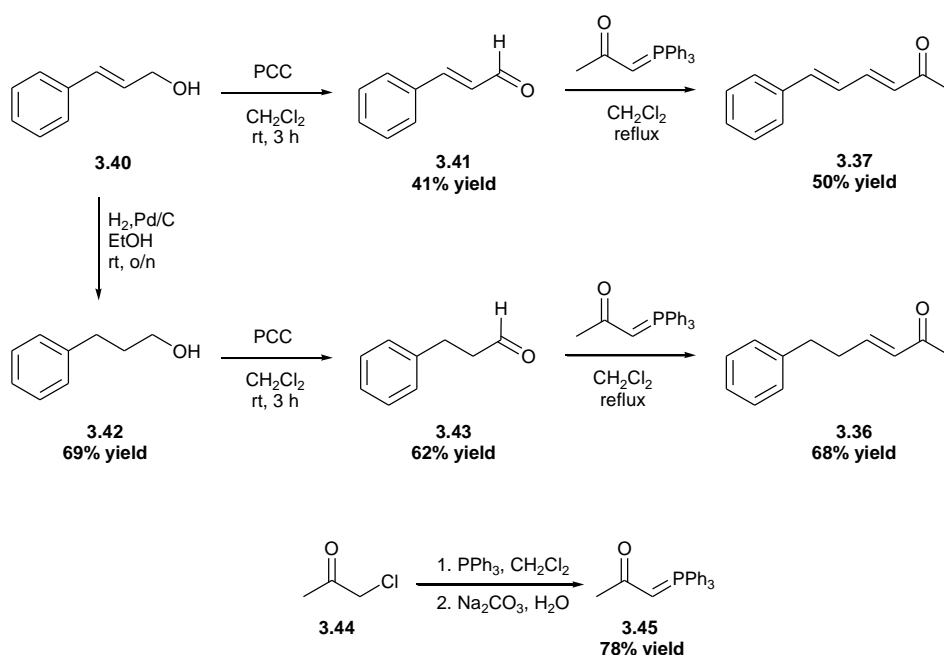
and the effects of varying reaction parameters should have parallel significance. Methyl vinyl ketone was chosen as the acceptor to keep the reaction fairly generic. Conveniently it is an inexpensive, commercially available reagent that is suitable for gas chromatography.

In applying potassium styryltrifluoroborate and MVK under rhodium catalysed conditions a number of possible products were considered as shown in Scheme 3.10. With literature reports suggesting isomerisation may occur, isomers **3.35** and **3.36** were considered potential products along with diene **3.37**. Competing homocoupling and protodeboronation products **3.38** and **3.39** are also likely. As such, these compounds were synthesised in order to obtain their standard GC retention times.



Scheme 3.10

Styrene, (**3.39**) the product of protodeboronation, is conveniently commercially available. Conjugate addition product **3.34** and isomer **3.35** were synthesised using rhodium catalysed addition methods. Isomer **3.36** and diene **3.37** were accessed from cinnamylalcohol as shown in Scheme 3.11. Fortunately, homocoupled product **3.38** had been isolated as a by product during addition reactions.

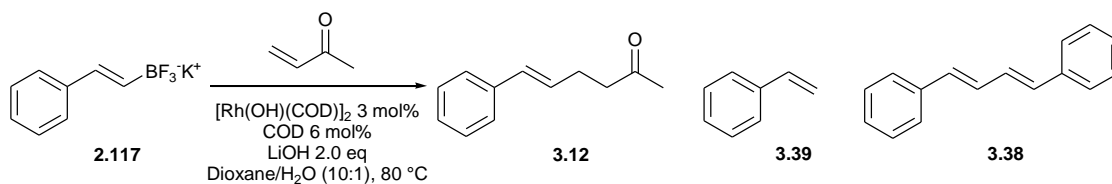


Scheme 3.11

For the GC study, our initial rhodium catalysed conditions were 3 mol% $[\text{Rh}(\text{OH})(\text{COD})]_2$, 6 mol% cyclooctadiene, enone at 0.13 M in dioxane/water 10:1 at 80 °C. 2.0 equivalents of base were used as current literature suggested that 1.0 equivalent is used to turn over the catalytic cycle, while the other hydrolyses the trifluoroborate to the transmetallating species. 2.0 equivalents of organoboron were employed and the data manipulated such that 100% formation of protodeboronation equates to 1.0 equivalent (the excess) of organoboron, any greater than 100% should also equate to a reduced product yield. In addition, homocoupled product requires 2 molecules of organoboron reagent therefore every 1% homocoupled product is equal to 2% organoboron, *ie.* 100% homocoupling relates to complete consumption of the 2.0 equivalents organoboron reagent.

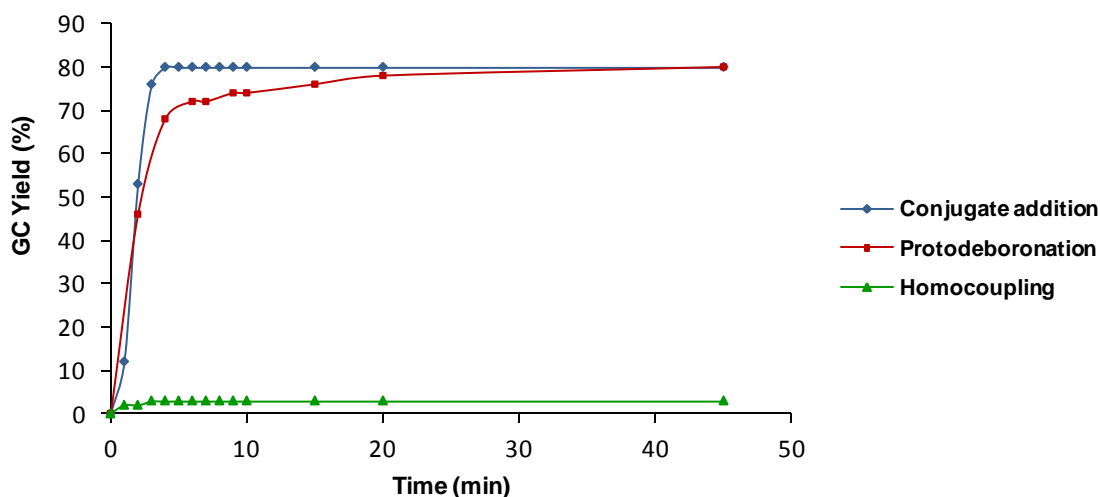
R factors and standard retention times for the potential products were determined. The standard conjugate addition procedure was followed and aliquots taken as the reaction progressed. Aliquots were immediately diluted with 1,4-dioxane to standard concentrations and filtered before analysis by GC.

Under the initial conditions described in Scheme 3.12, an interesting reaction profile (Graph 3.1) was produced.



Scheme 3.12

Initial rhodium catalysed conjugate addition conditions at 0.13 M



Graph 3.1

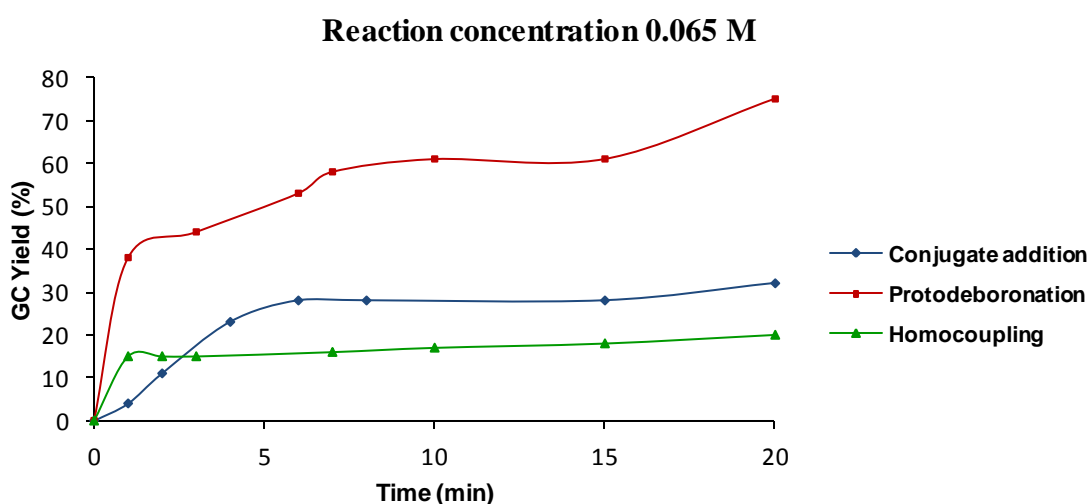
The rate of the conjugate addition reaction of potassium styryltrifluoroborate to methyl vinyl ketone was very fast and there was minimal change after the first 5 minutes. The abrupt stop in conjugate addition formation at 4 minutes could be a result of catalyst degradation or more likely, the reaction was complete at 80% conjugate addition. This indicates there is significant error which could be owing to the loss of volatile methyl vinyl ketone through the pierced rubber septum, combined with experimental error using small scale reactions.

At 4 minutes protodeboronation reached 70% and thus, considering the error, the majority of the excess organoboron had been consumed alongside formation of the desired product. Homocoupling was negligible and given the potential error, is insignificant.

3.4.4 Concentration Study

Conjugate addition reactions typically employ 10:1 organic solvent/water at 0.05-0.3 M concentrations. It is likely that the initial reaction concentration could have a profound effect on the initial reaction rates. Thus the reaction was followed at 0.065 M and 0.26 M with respect to MVK.

Reducing the reaction concentration to 0.065 M afforded the reaction profile demonstrated by Graph 3.2. Interestingly, conjugate addition was superseded by protodeboronation and in the time taken to complete 30% conjugate addition, the excess equivalent of potassium trifluoroborate salt had been completely consumed by side reactions. In a dilute reaction mixture with excess organoboron, it is more likely that the active transmetallated species will react with water to form protodeboronation rather than the desired methyl vinyl ketone. Or, since conjugate addition is very slow transmetallation may be slower in more dilute reactions and protodeboronation could be occurring predominantly through hydrolytic pathways.

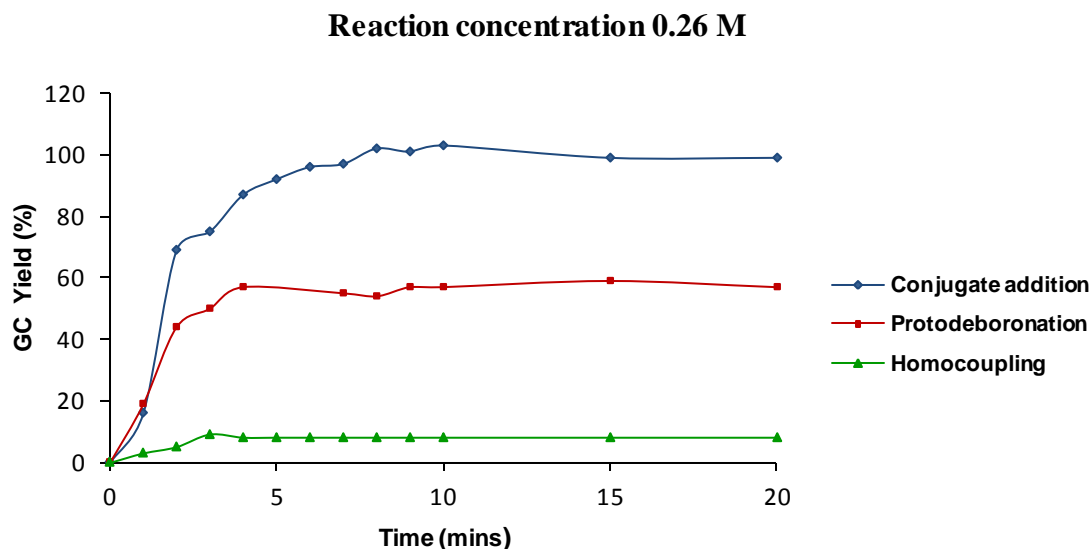


Graph 3.2

The undulations in the lines give an indication of the error in the data which would suggest error bars could be around $\pm 10\%$. Considering this inaccuracy, homocoupling again occurred minimally.

Alternatively, increasing the concentration to 0.26 M had a contrasting effect, as demonstrated by the product distribution in Graph 3.3. In a more concentrated solution, the active transmetallated rhodium species has a greater chance of reacting with MVK to afford complete conversion of conjugate addition within 10 minutes. A significant

proportion of the excess equivalent of organoboron is also simultaneously consumed *via* side reactions.



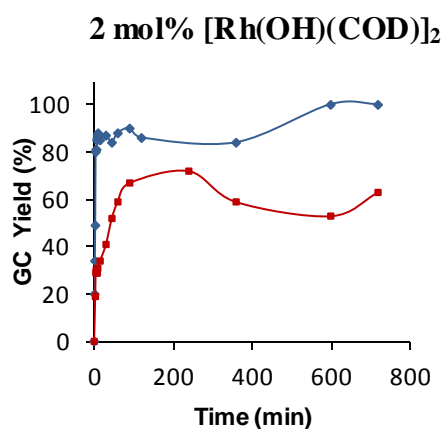
Graph 3.3

Higher reaction concentrations are preferable to facilitate the desired reaction over side reactions. Unfortunately, the problem lies in poor solubility of other potassium alkenyl trifluoroborate salts in more concentrated solutions. The solubility of all reagents can become restricted in some cases and thus the more practically suitable concentration is usually between 0.13 M and 0.26 M.

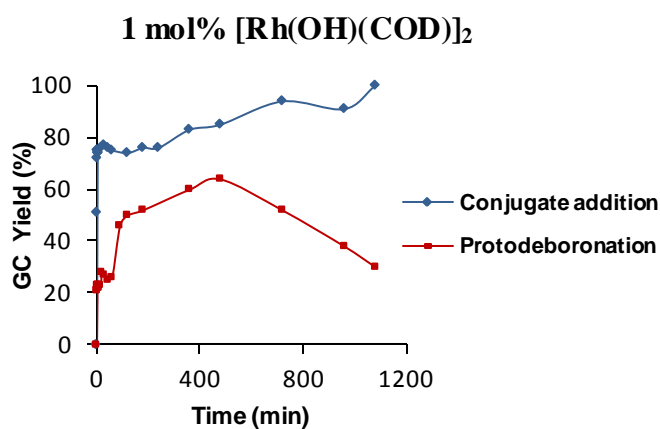
It is clear that concentration alone is not sufficient to suppress protodeboronation and for this reason it is also important to investigate the effects of other parameters. In general dilute reactions favour side reactions, predominantly protodeboronation.

3.4.5 Catalytic loading study

The initial 3 mol% catalyst is a high rhodium loading (6 mol%). Where possible it is useful to reduce the catalytic loading to reduce the cost of the reaction. As such the reaction was followed at 2 mol% and 1 mol% catalytic loadings (4 mol% and 2 mol% rhodium respectively) at reaction concentration 0.13 M. The reaction profiles, Graph 3.4 and Graph 3.5 indicate that lower catalytic loadings favour desired conjugate addition over protodeboronation and facilitate full conversion, albeit over longer reaction times.



Graph 3.4



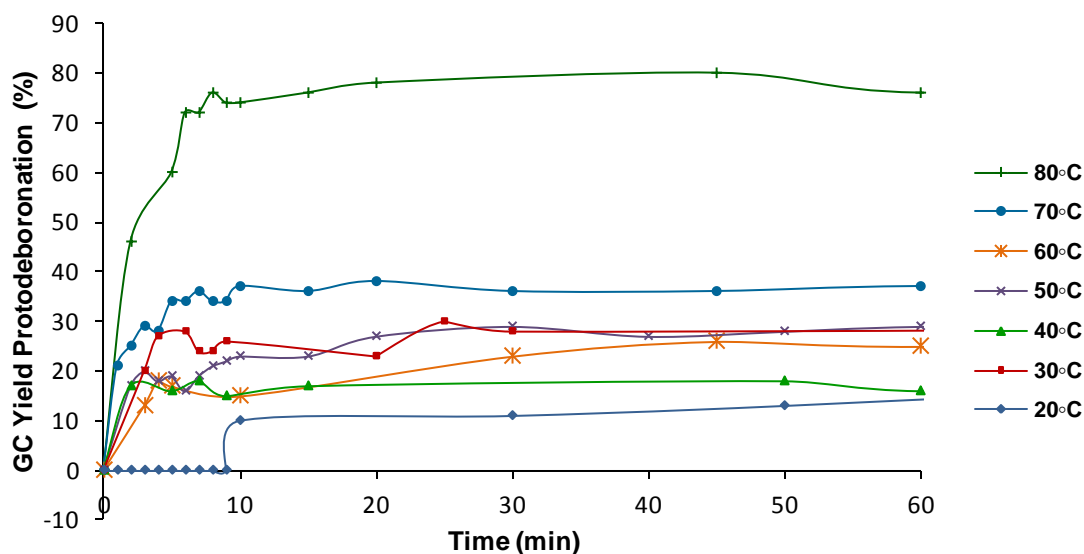
Graph 3.5

The initial rate of conjugate addition is fast in both reactions; at least 70% conversion is reached within several minutes. However, several hours are required to complete full conversion. The formation of protodeboronation is gratifyingly slower than the desired reaction. At lower catalytic loadings there is a lower concentration of active catalyst. It would appear that this limits the amount of excess active catalyst available to consume the organoboron reagent. The decline in protodeboronation after several hours using 1 mol% catalyst could be a result of styrene polymerisation or loss owing to its volatility. From a synthetic perspective, it is encouraging to find that lower catalytic loadings are beneficial for successful conjugate addition reactions with potassium alkenyl trifluoroborates.

3.4.6 Temperature study

Until recent years, standard conditions for conjugate addition required heating to 110 °C. Our experiments so far have been conducted at 80 °C. Recent publications have demonstrated successful reactions at room temperature and reported low temperatures reduce isomerisation and protodeboronation to improve product yields. Indeed, following the reaction at 20 °C intervals from room temperature up to 80 °C highlighted a very interesting trend that protodeboronation becomes a major problem at higher temperatures; significant protodeboronation was not observed at temperatures 70 °C or below (Graph 3.6). Between 30 °C and 60 °C protodeboronation was observed at similar levels, within the error of $\pm 10\%$.

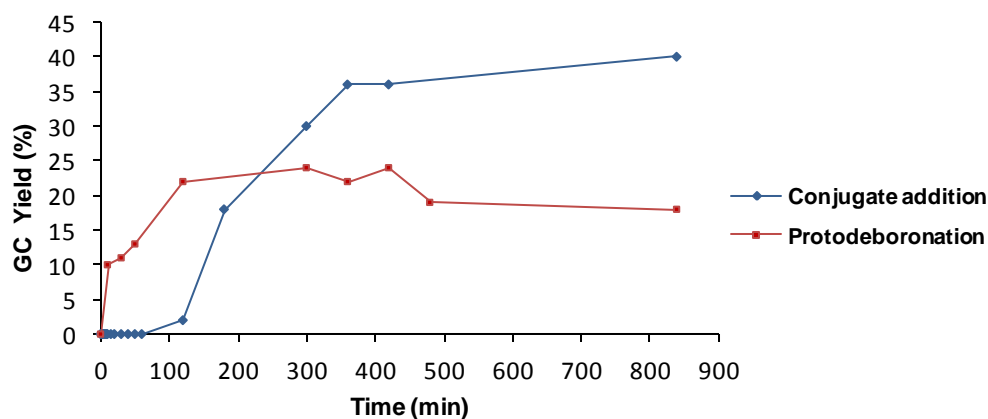
Protodeboronation in the rhodium catalysed conjugate addition reaction at different temperatures, at 0.13 M using 3 mol% catalyst



Graph 3.6

Also noteworthy is that no homocoupling was not observed at lower temperatures. Unfortunately, although less protodeboronation occurred at lower temperatures conjugate addition was also slower. For example, while some conjugate addition occurred at room temperature, there was a significant lag time of 2 hours before conjugate addition product began forming, but only a 10 minute lag time before protodeboronation started occurring (Graph 3.7). This lag time could be owing to slow hydrolysis of the potassium trifluoroborate to the active transmetallating species, slower active catalyst formation and slower transmetallation. After 14 hours, conjugate addition had only reached 40% conversion.

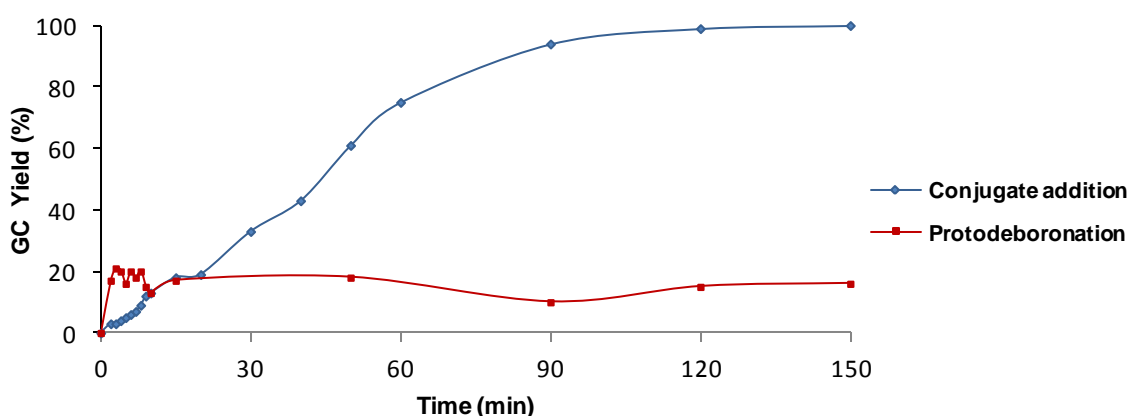
Reaction Profile at room temperature



Graph 3.7

There is a necessary balance between temperature and time, lower temperatures reduce protodeboronation, but excessive reaction times would be needed for less reactive enones. An elegant reaction profile, Graph 3.8 at 40 °C, demonstrates the slower reaction rate, but complete reaction in under 3 hours with minimal protodeboronation. It also indicates one of the main problems observed, that protodeboronation occurs faster than conjugate addition until conjugate addition begins to take place, at which point it suppresses protodeboronation. This could be owing to slower initial formation of the active catalytic species required for conjugate addition over protodeboronation at lower temperatures.

Reaction Profile at 40 °C



Graph 3.8

From the data obtained, the initial rates were obtained for conjugate addition and protodeboronation by assuming first order kinetics. Values were manipulated in terms of decreasing MVK concentration ($[MVK]$) for conjugate addition and decreasing concentration of potassium trifluoroborate ($[RBF_3K]$) for protodeboronation. Using data points over the first several minutes at each temperature, time was plotted against $\ln[RBF_3K]$ to obtain straight line plots with gradient = $-k$. Table 3.1 contains the rate constant k at each temperature for conjugate addition and protodeboronation.

The rate of protodeboronation is always slower than the rate of conjugate addition, increasingly so as temperature increases.

Temperature (°C)	Conjugate addition rate constant k (s ⁻¹)	Protodeboronation rate constant k (s ⁻¹)
30	0.0066	0.0064
40	0.0107	0.008
50	0.0191	0.0101
60	0.0212	0.016
70	0.0665	0.0254
80	0.2484	0.0329

Table 3.1

Important thermodynamic parameters are accessible through the Eyring equation (Eq. 3.1). This expression is based on transition state theory and describes the temperature dependence of rate constants.

$$k = \frac{k_B T}{h} \times e^{-\frac{\Delta H^\ddagger}{RT}} \times e^{\frac{\Delta S^\ddagger}{R}} \quad (\text{Eq. 3.1})$$

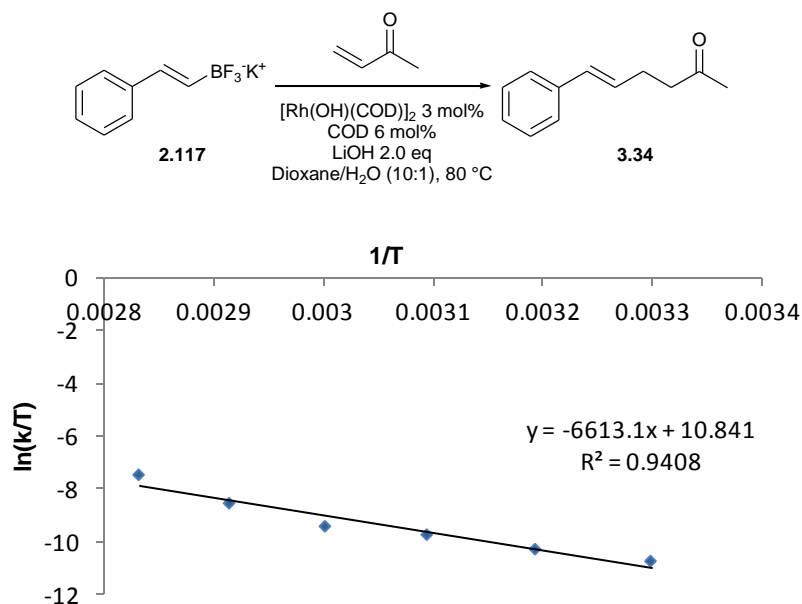
This can be rearranged to the linear form, Eq. 3.2 where k = reaction rate constant, T= absolute temperature, ΔH^\ddagger = enthalpy of activation, R= gas constant, k_B = Boltzmann constant, h = Planck's constant, ΔS^\ddagger = entropy of activation.

$$\ln \frac{k}{T} = \frac{\Delta H^\ddagger}{RT} + \ln \frac{k_B}{h} + \frac{\Delta S^\ddagger}{R} \quad (\text{Eq. 3.2})$$

By plotting the logarithmic value of the rate constant divided by temperature, $\ln(k/T)$, against the inverse temperature ($1/T$) a straight line plot can be obtained. The gradient ($-\Delta H^\ddagger/R$) can be used to calculate the enthalpy of activation and the intercept ($\ln k_B/h + \Delta S^\ddagger/R$) can be used to derive the entropy of activation.

Graph 3.9 displays the Eyring plot for conjugate addition, from which the activation enthalpy was calculated as 55 KJmol⁻¹. The activation entropy for the reaction was -107 Jmol⁻¹K⁻¹.

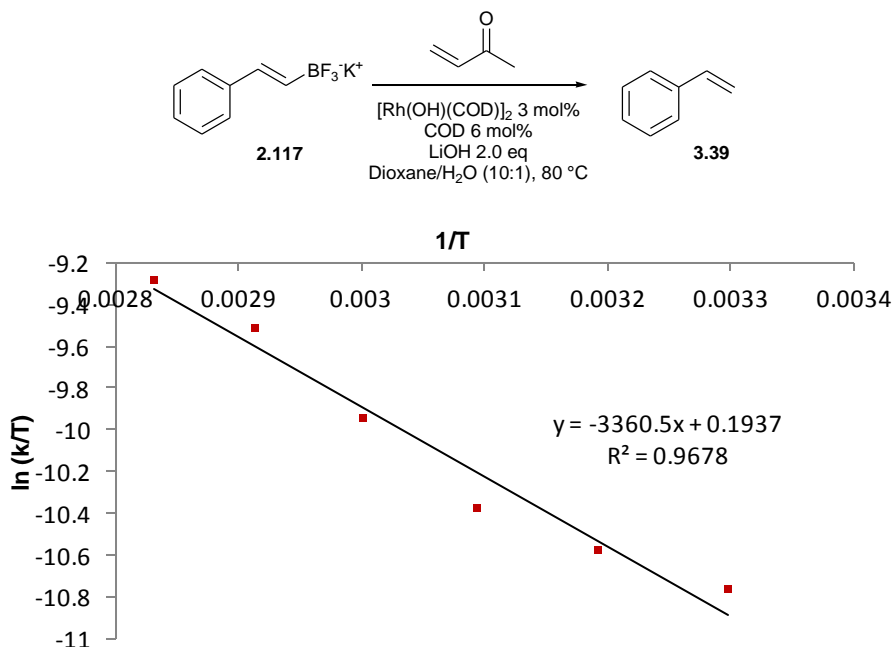
Eyring Plot for the Conjugate Addition Reaction



Graph 3.9

Graph 3.10 displays the Eyring plot for the protodeboronation reaction, from which the activation enthalpy was calculated as 28 KJmol⁻¹. The activation entropy for the reaction was -196 Jmol⁻¹K⁻¹.

Eyring Plot for the Protodeboronation Reaction



Graph 3.10

Owing to fast initial rates these values are likely to contain a high degree of error, but give an indication of the order of magnitude. The enthalpy of activation for conjugate

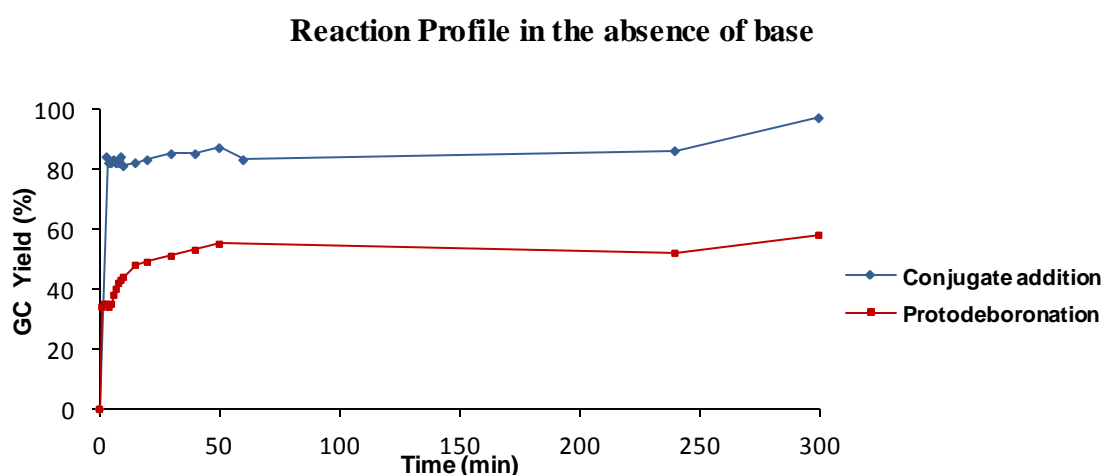
addition is higher than that for protodeboronation, so protodeboronation is kinetically favoured, but conjugate addition is thermodynamically favoured. This explains the reaction profile and lag time observed at 40 °C.

The entropy of activation is more negative for protodeboronation than conjugate addition, indicating an increase in order by formation of the transition state.

3.4.7 Base Study

The role of base in the reaction has been reported as two-fold. It is required to act as a ligand to aid formation of the active rhodium-hydroxy species and facilitate catalyst turnover. Until recently, it has also been thought that base is required for the hydrolysis of trifluoroborate, to the transmetallating species $\text{BF}_n\text{OH}_{3-n}$. For the purposes of this study to correlate to later work a number of bases were chosen and their reactions followed by GC.

The reaction profiles obtained were very similar. Around 40% protodeboronation initially formed, but with limited increase over the course of the reaction. Conjugate addition reached 100% conversion within 5 minutes where 2.0 equivalents of base were present. Perhaps the most interesting profile was when no base was present, as shown in graph 3.11.



Graph 3.11

Both conjugate addition and protodeboronation initially occur quickly as in the reactions with base added. Within 5 minutes 80% conversion to conjugate addition is

reached, but the remaining 20% takes a further 5 hours to complete. This suggests the reaction doesn't require base, but the role of base is to prevent catalyst decomposition. From this reaction, turnover number (TON) is 42¹². Also interesting is the continued increase in protodeboronation, which was not evident when base was present. This is possible evidence for protodeboronation occurring *via* an uncatalysed pathway facilitated by less basic reaction mediums.

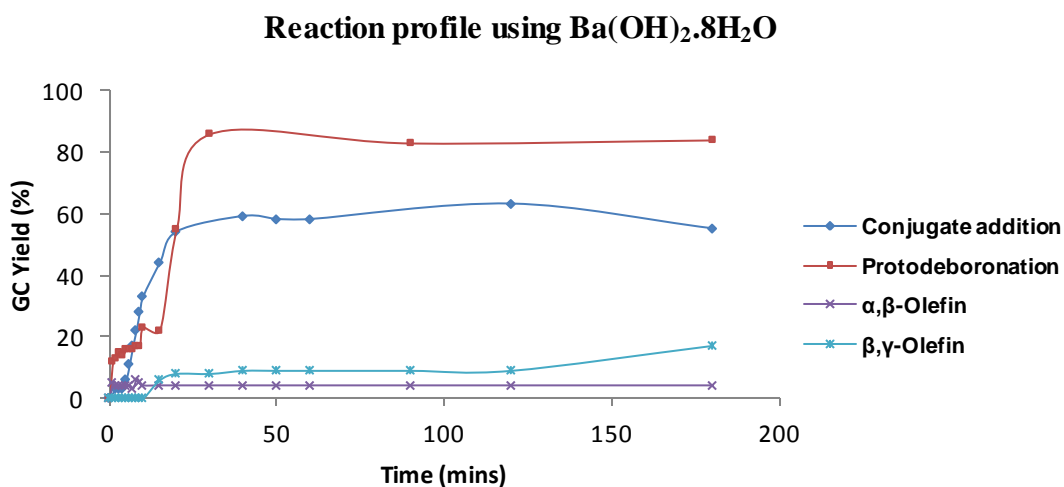
It appeared most bases had minimal influence on the initial rate of conjugate addition (Table 3.2). LiOH, KOH, K₂CO₃ and K₃PO₄ are roughly the same given the error in the results.

Base	Rate of conjugate addition (k, s ⁻¹) ^a
None	n.d ^b
LiOH	1.30
KOH	1.34
K ₂ CO ₃	0.96
K ₃ PO ₄	1.3
Ba(OH) ₂ .8H ₂ O	0.05 ^c

a) over the first 5 data points b) not enough data points for accurate calculation, c) minimal competing transposition also occurring

Table 3.2

The rate of conjugate addition using Ba(OH)₂.8H₂O was significantly slower owing to significant protodeboronation and some formation of other isomers (graph 3.12).



Graph 3.12

Miyaura has reported that transmetallation of borates to palladium is affected by bases and counter cations.¹³ There is believed to be a free equilibrium between boronic acids and the hydroxyborate anion; as basic strength increases ($\text{OH}^- > \text{MPO}_4^- > \text{MCO}_3^- > \text{HCO}_3^-$) the concentration of the hydroxyborate increases which would increase transmetallation if this is the active transmetallating species, or decrease transmetallation if boronic acid is the transmetallating species. Also critical is the counter ion which decreases OH stability down the group ($\text{Cs}^+ < \text{K}^+ < \text{Na}^+ < \text{Li}^+$). Our results indicate little difference is made to conjugate addition by basic strength or group 1 counter ions.

They also suggest that transmetallation is increased by counter ions that highly stabilise halide ions, in particular those able to form insoluble salts such as BaX_2 ($\text{Ag}^+ > \text{Tl}^+ > \text{R}_4\text{N}^+ > \text{Ba}^{2+} > \text{Cs}^+ > \text{K}^+$). This does not appear to be the case from our results, which may suggest base is not responsible for trifluoroborate hydrolysis.

Generally protodeboronation was suppressed by the addition of base; after initial formation within the first 2 minutes of the reaction, further increase in protodeboronation was negligible. Too few data points were available for accurate rate constant determination. The exception to this was $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$, which resulted in 86% protodeboronation (graph 3.12) at a rate $k = 0.01 \text{ s}^{-1}$. From examination of the reaction profiles and yields of protodeboronation, bases in order of their ability to minimise protodeboronation is as follows:

Less
protodeboronation $\text{KOH} = \text{K}_3\text{PO}_4 = \text{K}_2\text{CO}_3 > \text{LiOH} > \text{none} > \text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ More
protodeboronation

The counter ion plays a more interesting role than the basic strength for protodeboronation; lithium hydroxide enabled more protodeboronation than weaker potassium bases.

These results indicate that the faster conjugate addition occurs, the more protodeboronation is suppressed. It is clear the counter ion has an effect here as despite a high rate for conjugate addition using LiOH, protodeboronation is not as well suppressed. It has been reported lithium trifluoroborate salts are less stable than potassium salts. Barium also has an interesting effect, there is no suppression of protodeboronation. Barium trifluoroborate salts would be very unstable from an

unbalanced charge. Also using $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$, other product isomers were observed in small quantities.

Since this work triethylamine has been employed in conjugate additions to facilitate lower reaction temperatures, thereby reducing protodeboronation.³ It would be interesting to compare this in the study in the future.

3.4.8 Solvent Study

Similarly to bases, reports have suggested that solvents can affect protodeboronation. For example, in a large scale rhodium catalysed conjugate addition reaction, water was replaced by isopropanol to reduce the protodeboronation of 3,5-difluorophenylboronic acid.¹⁴

Results were mixed and inconclusive. It is likely solvent effects are affected by substrate solubility and trifluoroborate hydrolysis as much as their own effects on the reaction. The key result was that in anhydrous polar, aprotic solvents such as THF and dioxane, lag times for conjugate addition were coupled with fast protodeboronation. Contrastingly, in anhydrous polar protic solvents, there is no lag time for conjugate addition, but competing protodeboronation was still an issue.

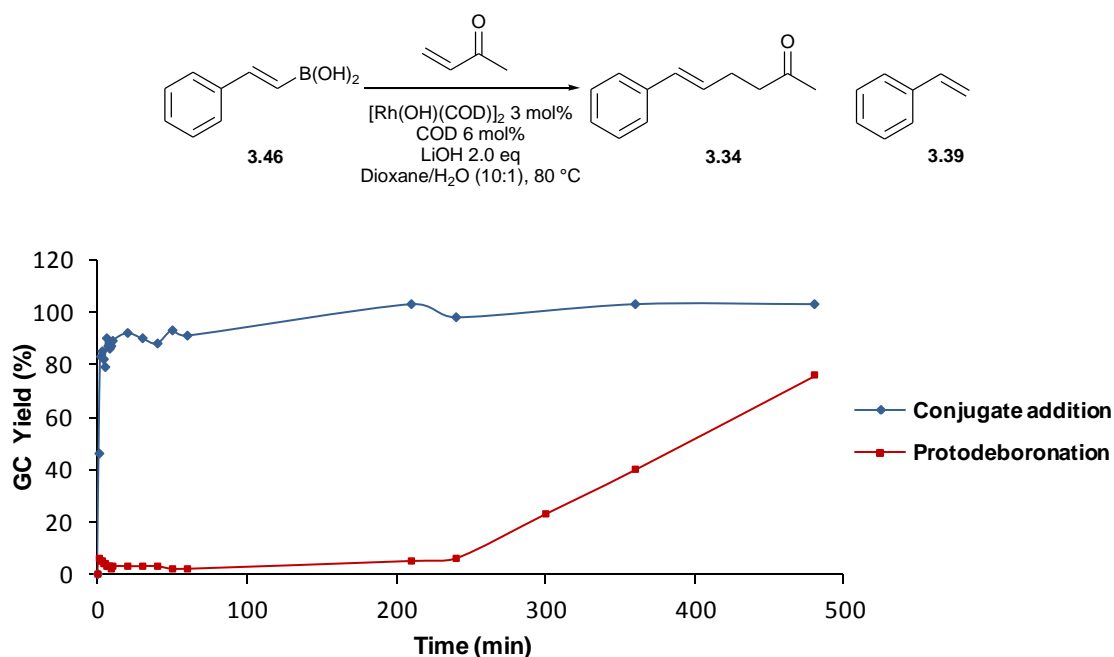
3.4.9 Boronic acid compared to trifluoroborate

Aryl boronic acids are frequently used in the conjugate addition reaction, but owing to the limited stability of alkenylboronic acids in air, alkenyl trifluoroborate salts are more useful. Claims have been made in the past that trifluoroborates are more reactive than boronic acids.

To determine whether trifluoroborates and boronic acids have different reactivities or whether potassium trifluoroborates are 'protected' boronic acids, the reaction was followed by GC using styryl boronic acid (Graph 3.13). 100% conversion was achieved, but a longer reaction time was necessary. 90% conversion was achieved after 6 minutes, but the remaining 10% required 3 hours.

Most interestingly less protodeboronation was observed over the course of the reaction, in fact, it was suppressed until the conjugate addition reaction had reached completion.

Reaction profile using styryl boronic acid



Graph 3.13

Both boronic acid and trifluoroborate reagents successfully afford conjugate addition. This suggests that the active transmetallating species is equally as accessible through the boronic acid and trifluoroborate, which is evidence to suggest that potassium trifluoroborate salts are protected boronic acids. For boronic acids, minimal protodeboronation occurs until conjugate addition is complete. It is interesting to note at this stage that potassium trifluoroborate salts appear to undergo more facile protodeboronation. Either an uncatalysed mechanism occurs or the metal catalysed mechanism is promoted when trifluoroborates are employed. If HF is produced as a by product of trifluoroborate hydrolysis to the transmetallating species, it would follow this acid could promote protodeboronation. Alternatively a mixed species $\text{RBF}_n(\text{OH})_{3-n}$ could be transmetallating to rhodium for faster metal catalysed protodeboronation. The different results obtained for boronic acids and trifluoroborates could also be owing to the formation of different catalysts within each reaction. For example, Csaky and co-workers have previously speculated the formation of the anionic rhodium complex $[\text{RhcodFRL}]^-$ in the presence of fluoride ions.⁸

Unfortunately, despite this seemingly attractive profile, the application of alkenylboronic acids is limited by their poor stability as isolatable reagents and thus potassium alkenyl trifluoroborates remain more preferable. In addition, further information is needed to more fully understand potassium trifluoroborate hydrolysis and protodeboronation.

3.4.10 Conclusions

The key conditions that affect protodeboronation are reaction concentration, temperature and catalytic loading. Concentrated reactions favour conjugate addition over side reactions. Protodeboronation is favoured in dilute reactions. The ideal concentration for practical use is between 0.13 M and 0.26 M. Decreasing catalytic loading increases reaction time, but enables full conversion by decreasing protodeboronation.

Temperature has a critical effect on both conjugate addition and protodeboronation. Protodeboronation is reduced at lower temperatures, but conjugate addition has a higher activation enthalpy than protodeboronation, which results in a time lag at lower temperatures. If active catalyst systems are employed lower temperatures would be preferable.

Base is crucial to prevent catalyst degradation and complete conversion in shorter reaction times, but different bases affect conjugate addition and protodeboronation differently. Potassium is the most effective counter ion to limit protodeboronation, possibly owing to more stable trifluoroborate salts and a slower release of boronic acid.

These initial studies indicate that the transmetallating species is accessible from boronic acids and trifluoroborates, so the trifluoroborate could be slowly releasing boronic acids within the reaction. Trifluoroborate salts undergo faster protodeboronation than boronic acids in the reaction, possibly owing to a hydrolytic-uncatalysed pathway or an alternative catalytic species. Further mechanistic study is required to determine the pathway of protodeboronation and gain further insights into potassium trifluoroborate hydrolysis.

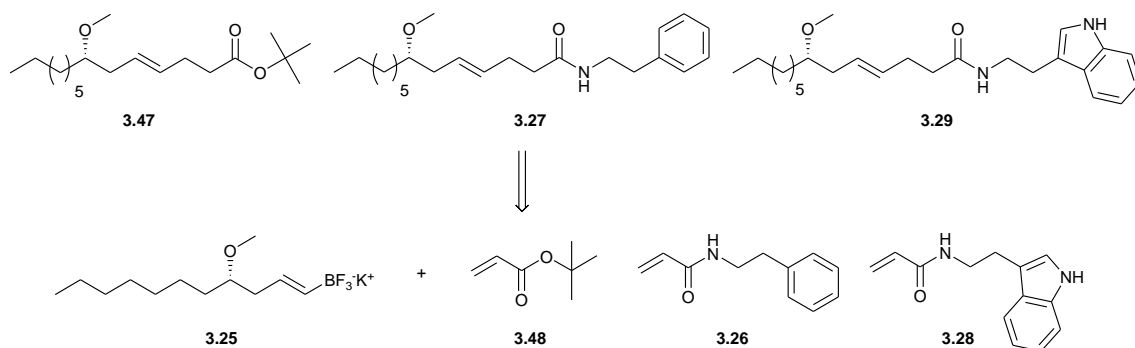
3.5 Olefin transposition

3.5.1 Introduction

In several applications of alkenylboronates in rhodium catalysed conjugate addition reactions there have been reports of some olefin isomerisation. In some ways this is not surprising as rhodium is known to catalyse olefin isomerisation.¹⁵ However, there has been limited detail of the isomers formed and it is often seen as a problem that has not been addressed. On the other hand, olefin transposition within the rhodium catalysed addition of potassium alkenyl trifluoroborate salts has great potential; if olefin transposition can be selectively controlled this would be a valuable new reaction to gain access to new and challenging products.

3.5.2 Previous work

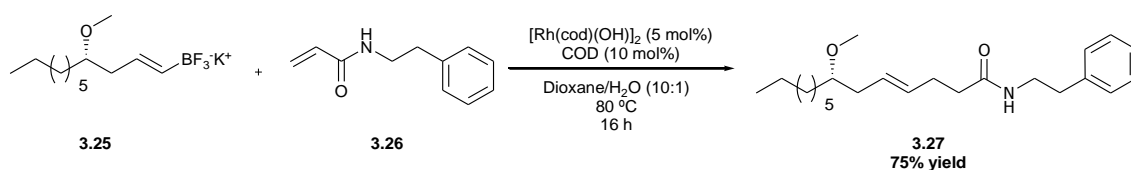
Previous work in the Frost group involved the application of enantiopure alkenylboronate **3.25** under rhodium catalysed conditions towards the novel synthesis of natural products hermitamides A **3.27** and B **3.29** and the structural building block lyngbic acid **3.47** (Scheme 3.13).¹⁶



Scheme 3.13

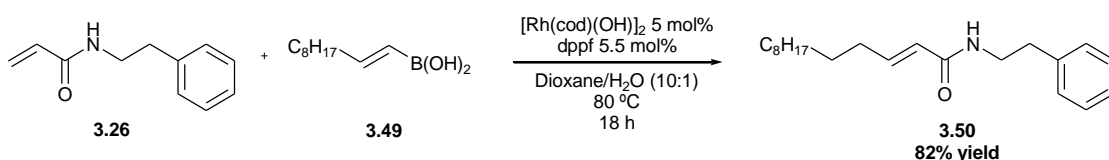
The alkenylpinacolboronic ester was unreactive in the conjugate addition under a variety of conditions. Alkenylboronic acids were also met with limited success owing to difficulty in their isolation as reagents and poor yields upon their application. The current literature precedent for the conversion of pinacolboronic esters to trifluoroborate salts and their success as organoboron donors prompted the synthesis and application of the corresponding potassium alkenyl trifluoroborate salts.

Towards the synthesis of hermitamide A **3.27** (Scheme 3.14), a rhodium-diene catalyst system successfully generated conjugate addition product **3.27**. In order to improve the yield, optimisation was undertaken and the catalytic loading increased to 5 mol% dimer.



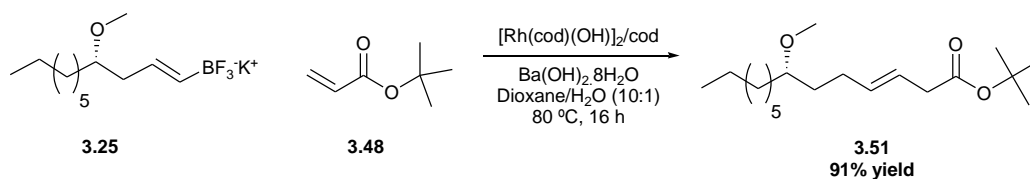
Scheme 3.14

During the course of the optimisation by employing decenyl boronic acid (**3.49**), a number of parameters were screened. An interesting result was observed by changing the ligand to dppf (Scheme 3.15). A new isomer was isolated where the olefin underwent transposition back into conjugation with the carbonyl forming α,β -olefin **3.50**.¹⁷



Scheme 3.15

When the successful conjugate addition conditions were applied in the synthesis of lyngbic acid, the yield was minimal. Initially a number of bases were screened and under the addition of 2.0 equivalents $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ an interesting isomer was isolated selectively in excellent yield (Scheme 3.16). Single isomerisation of the alkene had taken place towards the carbonyl, to generate β,γ -olefin **3.51**.



Scheme 3.16

Both isomer α,β -olefin **3.50** and β,γ -olefin **3.51** were confirmed by analysis of their 2D NMR spectra. Single changes in additives gave dramatically different results, which were not consistent when transferred to other substrates.

While evidence in the literature indicated the possibility for olefin isomerisation, these results highlighted the potential for olefin transposition under rhodium catalysed

conditions, but also the requirement to understand and control the transposition. If the reaction could be controlled to selectively generate each isomer as required, it would be a very useful process for the synthetic chemist.

3.5.3 Aims

To investigate and selectively control olefin transposition within the rhodium catalysed addition of potassium alkenyl trifluoroborate salts. To identify general and selective conditions, demonstrate the scope of reaction and determine a likely mechanism for the process.

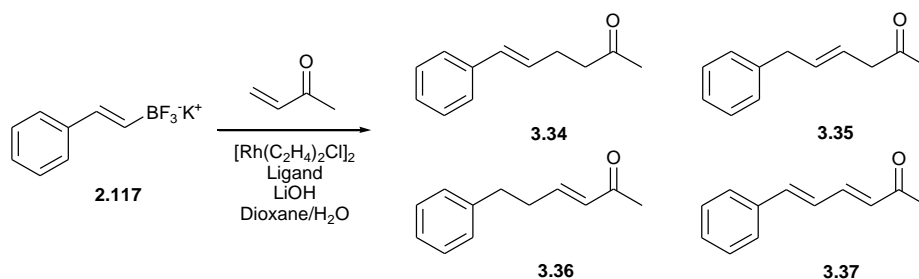
3.5.4 Initial Studies

During the previous work the ligand had demonstrated a profound effect on the reaction. In some cases $\text{Ba(OH)}_2 \cdot 8\text{H}_2\text{O}$ also affected the selectivity. Minor olefin transposition was also observed when $\text{Ba(OH)}_2 \cdot 8\text{H}_2\text{O}$ was employed in the GC.

Ligands are known to affect the enantioselectivity and regioselectivity of reactions. For example, Tropos directed the addition of aryl boronic acids to α,β -unsaturated ketones, from 1,4 to a double 1,4 + 1,2 addition with an excess of boronic acid.¹⁸ In a number of industrially important reactions there is a correlation between catalytic activity and the bite angle (P-M-P angle, β) of bidentate P-donor ligands.^{19,20,21,22} This is most evident in the rhodium-catalysed hydroformylation reaction where catalytic activity and regioselectivity are enhanced by wide bite angles ($\beta > 110^\circ$).^{23,24}

Wide bite angle phosphine,²⁵ bis-phosphine,^{26,27,28} phosphine-olefin,^{29,30} other phosphine^{31,32} and diene^{33,34,35,36,37,38,39} ligands have been developed in attempts to improve the activity and enantioselectivity of rhodium catalysed conjugate additions.

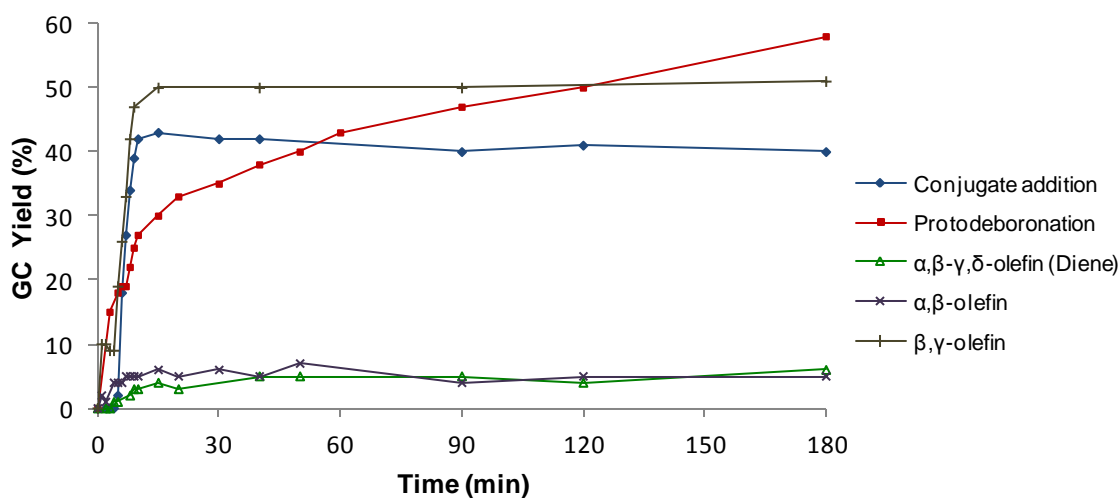
Therefore, we extended our GC studies to explore the effects of ligands on the rhodium catalysed addition of potassium styryltrifluoroborate to methyl vinyl ketone. Scheme 3.17 highlights the possible isomers, either conjugate addition **3.34** or olefin transposition to isomers **3.35**, **3.36** and **3.37**.



Scheme 3.17

Phosphine ligands have been moved away from in rhodium catalysed conjugate additions owing to the greater reactivity and enantioselectivity of enantiopure diene ligands. However, enantiopure phosphine ligands are cheaper and more commercially available. In the past BINAP has been frequently employed. Interestingly, in the literature examples where isomerisation had been reported, phosphine ligands, in particular BINAP were used. Graph 3.14 highlights the magnitude of the problem often faced and the complex mixture of products produced using BINAP in the rhodium catalysed addition of potassium styryltrifluoroborate to methyl vinyl ketone.

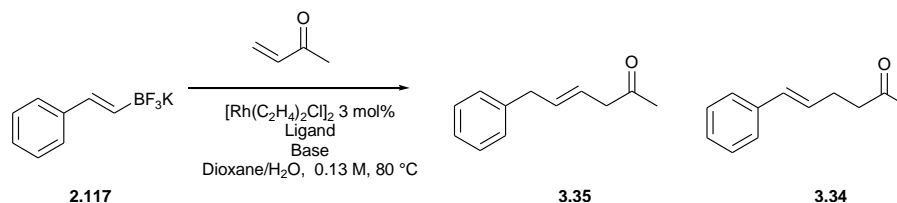
Product distribution when employing BINAP



Graph 3.14

Addition products conjugate addition (**3.34**), β,γ -olefin (**3.35**), α,β -olefin (**3.36**) and diene α,β - γ,δ -olefin (**3.37**) form in a 40:50:5:5 ratio. The excess organoboronate **2.117** is consumed by 60% protodeboronation. In light of this result, it is unsurprising isomerisation was reported, but not fully identified, in previous applications using BINAP as a ligand.

The reaction was followed by GC with a number of phosphine ligands. Table 3.3 summarises the isomeric ratios obtained. The ligand appears to be the crucial influencing additive for facilitating olefin transposition. While cyclooctadiene selectively afforded conjugate addition, phosphine ligands promote or enable transposition, but in many cases give isomeric mixtures.



Entry	Ligand	β_n^a	Conv. [%] ^[b]	3.35/3.34 ^[c]
1	COD	85 ^g	80	0:100
2 ^[d]	COD	85 ^g	>99	0:100
3	BINAP	92 ^h	90	50:40
4	MeDuPHOS	83 ^h	62	87:13
5	dpp-benzene	83 ^h	48	77:23
6	Sphos	-	70	10:60
7 ^[e]	PPh ₃	-	99	86:13
8 ^[e]	dppe	85 ^h	75	60:15
9	dppp	91 ^h	>99	86:14
10	dppb	98 ^h	<99	93:7
11 ^[f]	dppf	96 ^h	>99	95:5
12 ^[e]	d ⁱ ppf	100 ⁱ	74	100:0
13 ^[e]	d ^t bupf	104 ^j	21	15:6

[a] Natural bite angle [b] Conversion of substrate **2.117** into addition products was determined by GC on the crude reaction mixture after 30 minutes. [c] The ratio of addition products **3.35/3.34** was determined by GC on the crude reaction mixture after 30 minutes. [d] Reactions carried out at 0.26 M. [e] Conversion after 200 minutes [f] 4 % α,β -olefin was also observed products in a 91:5:4 ratio.[g] ref 40. [h] ref 41, [i] ref 42[j] ref43

Table 3.3

In terms of preference for transposition, dppb > dppp > dppe indicating that larger bite angles promote transposition. Curiously, triphenylphosphine had a similar selectivity to dppp despite being monodentate. Ferrocene based ligands (Figure 3.1) dⁱppf and dppf, with similar bite angles to dppb were similarly very selective towards transposition.

Selectivity towards transposition is highly dependent on medium bite angles $\sim 100^\circ$ and flexibility of the backbone. Ferrocenylphosphine ligands are particularly unique in their 3-dimensional conformational and rotational flexibility which allows them to achieve a range of bite angles as the reaction requires.⁴⁴ Dⁱppf was entirely selective towards β,γ -olefin, but the yield was restricted by competing protodeboronation. Dppf was highly selective for β,γ -olefin, and gratifyingly the rate of protodeboronation was dramatically decreased to afford the β,γ -olefin in high yield. D^tbupf enabled fast protodeboronation limiting the desired reaction. These results indicate the direct steric and electronic effects of the ligand also influence the reaction.

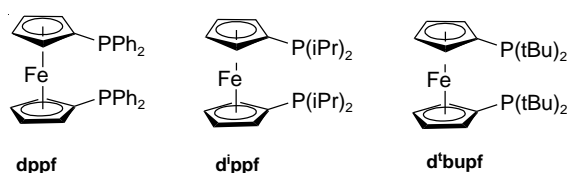


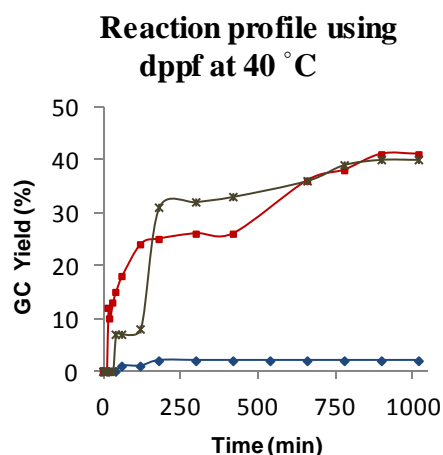
Figure 3.1

The reaction profiles were as useful as the product distributions. It has already been established that diene ligands provide greater reactivity than phosphine ligands for the conjugate addition of arylboronates. For example, a kinetic study by Hayashi and co-workers determined that $[\text{Rh}(\text{OH})(\text{cod})]_2$ was about 20 times more active than $[\text{Rh}(\text{OH})\text{binap}]_2$.⁴⁵ It was no surprise therefore that the rate of formation of conjugate addition is faster using cyclooctadiene compared to phosphine ligands.

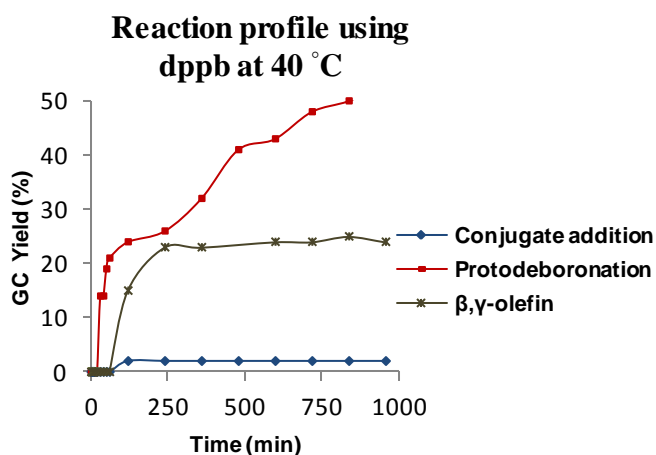
Not visible from Table 3.3, but apparent from the reaction profiles are slower initial rates and even a time lag of product formation in some, even very selective cases. This time lag could be owing to slower formation of the active rhodium-phosphine complex. In all examples employing phosphine ligands, protodeboronation was an increased problem, competing at a similar or greater rate than the desired reaction. Therefore it appears we have a problem in that while phosphine ligands are required for olefin transposition they also enable greater protodeboronation. This could be a synergistic or direct effect. Either a slower rate of desired reaction enables more protodeboronation, or phosphine ligands promote metal catalysed protodeboronation.

Owing to the success of dppf and dppb in achieving high selectivity and conversion towards β,γ -olefin a small temperature screen was conducted. For the transposition

reaction at lower temperatures, the rate of desired reaction was significantly reduced, using both dppf and dppb at 40 °C (Graph 3.15 and 3.16).

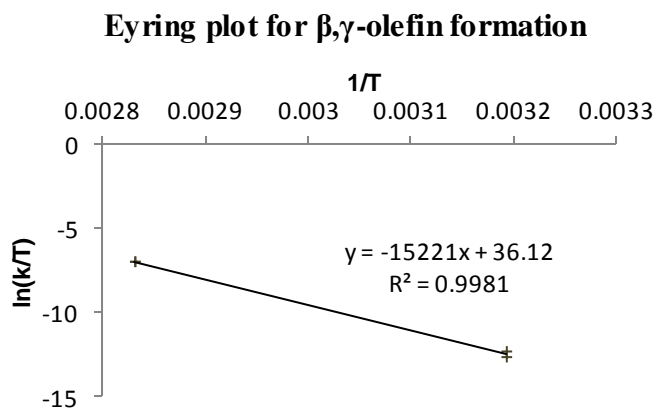


Graph 3.15



Graph 3.16

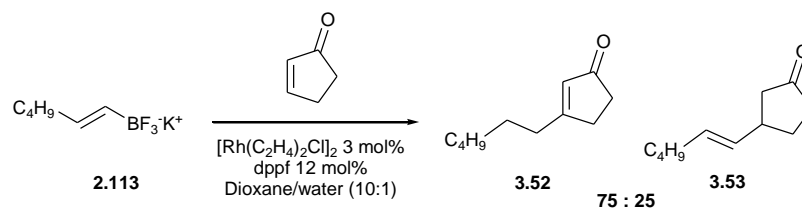
There may be a time lag before the desired reaction occurs during which time protodeboronation commences. Aside from the low conversion, less than 40% after 12 hours, the selectivity for transposition product β,γ -olefin is also reduced as minimal conjugate addition also forms. These can be explained by the slower formation of active rhodium-phosphine complex at lower temperatures and the lower activation enthalpy of protodeboronation and conjugate addition compared to β,γ -olefin formation. From Eyring plot 3.17, using rate constants from dppf and dppb at 80 °C and 40 °C, the enthalpy of activation for the formation of β,γ -olefin is 127 KJmol^{-1} , more than double that for conjugate addition. The activation entropy for the reaction is 103 $\text{Jmol}^{-1}\text{K}^{-1}$. With only 4 data points these values again contain significant error. A higher activation enthalpy for the formation of β,γ -olefin could suggest the mechanism is different from that of conjugate addition.



Graph 3.15

Therefore, high temperatures would be required to achieve olefin transposition with good selectivities, high conversions and practical reaction times.

Having achieved excellent β,γ -olefin selectivity with dppf, we considered applying the conditions to less reactive enones to test the generality of the reaction. Hexenyl potassium trifluoroborate (**2.113**) was reacted with cyclopentenone employing 3 mol% $[\text{Rh}(\text{C}_2\text{H}_4)\text{Cl}]_2$ and 12 mol% DPPF in dioxane/water 10:1 at 80 °C for 18 hours (Scheme 3.18).



Scheme 3.18

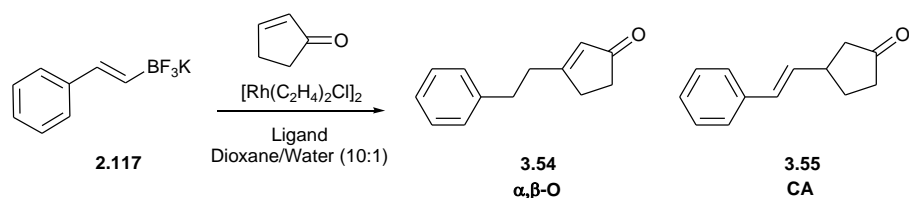
With this cyclic enone, transposition of the olefin occurs back into conjugation with the ketone to form α,β -olefin **3.52** in a 75:25 ratio with conjugate addition (**3.53**). Further optimisation was undertaken to improve the selectivity and yield of the α,β -olefin transposition focussing on cyclic enones.

3.5.5 Aims

Optimise rhodium catalysed conditions for selective α,β -olefin transposition and demonstrate the scope of α,β -olefin and β,γ -olefin transposition.

3.5.6 α,β -Olefin transposition optimisation

Our crucial finding had been that the ligand controlled the selectivity of transposition. To confirm dppf was the optimum ligand for α,β -olefin transposition using cyclic enones, a range of ligands were tested with 12 mol% ligand and 3 mol% $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (Table 3.4). The ratios of α,β -olefin (α,β -O) **3.54** to the conjugate addition product (CA) **3.55** were determined by ^1H NMR of the crude reaction mixtures. These values are not relative to conversions owing to removal of unreacted cyclopentenone *in vacuo* during work-up.



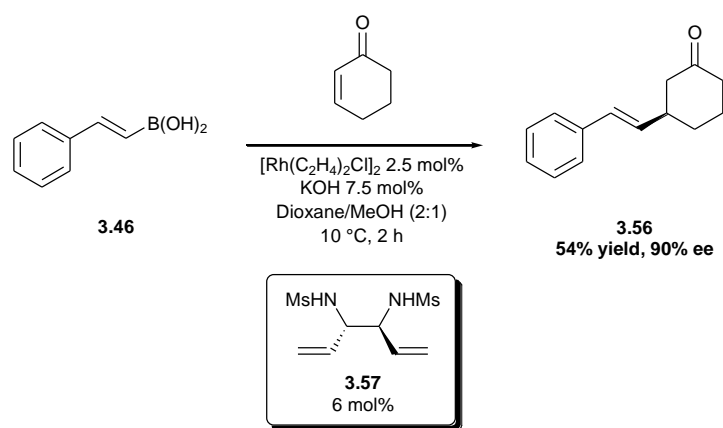
Ligand	$\beta_n^{a,f}$	% Products ^b	
		$\alpha,\beta\text{-O}$	CA
dppf	96	83	17
d ⁱ ppf	100	95	5
d ^t bupf	104	0	0
COD	85	7	93
BINAP	92	61	39
PCy ₃	-	40	60
John Phos	-	15	85
SPhos	-	28	72
Xantphos	111.7 ⁴⁶	0	0

^a natural bite angle, ^b crude isomeric ratio determined by ¹H NMR

Table 3.4

The results were in agreement with our previous findings; diene ligands favour conjugate addition whereas phosphine ligands promote transposition, forming mixtures of isomers in most cases. Successful olefin transposition is facilitated by bidentate phosphine ligands that possess a flexible backbone and the ability to access a range of bite angles between 90° and 100°. Similarly to the GC results, dppf achieved good selectivity, dⁱppf was even more selective for α,β -olefin transposition, but d^tbupf afforded no desired product or conjugate addition. The steric and electronic nature of the phosphine also affects the reactivity and selectivity. Despite lower selectivity, dppf allows less protodeboronation and therefore higher yields.

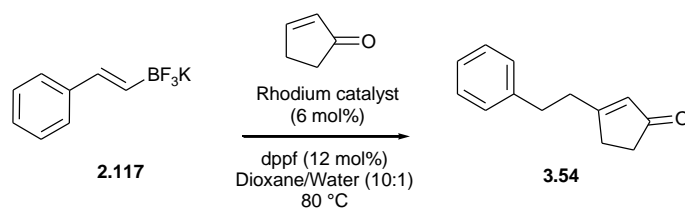
Flexible diene ligands such as **3.57** have been synthesised by Du and co-workers to successfully afford high enantioselectivities and yields in the conjugate addition of arylboronic acids.⁴⁷ In the addition of styrylboronic acid **3.46** to cyclohexenone in Scheme 3.19, the conjugate addition product **3.56** has high enantioselectivity, but only 54% yield.



Scheme 3.19

While no isomerisation is noted to account for the lower yield, the flexible backbone and reported fast coordination/dissociation of the ligand to the rhodium are features that promote olefin transposition. This could present a future challenge to design a flexible diene ligand that will facilitate olefin transposition at lower temperatures to improve the reactivity of less reactive enones and combat the problem of protodeboronation.

In a screen of rhodium catalysts, $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ maintained clean crude NMR spectra and most effectively achieved the desired transformation using dppf as the ligand (Table 3.5). This is owing to its ability to form the active Rh-dppf complex through efficient exchange with ethylene. It is interesting that cationic catalysts favor conjugate addition even in the presence of dppf.

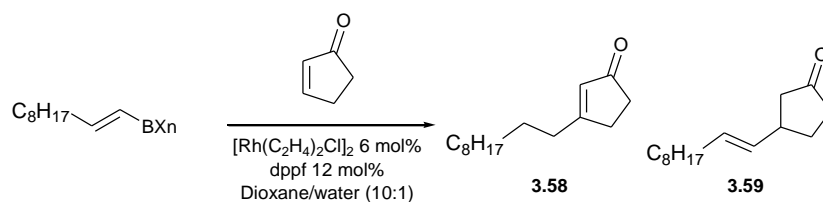


Catalyst	%Products ^a	
	α,β -O	CA
$[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$	83	17
$\text{Rh}(\text{COD})_2\text{BF}_4$	40	60
$\text{Rh}(\text{COD})_2\text{PF}_6$	12	88

^a determined by ^1H NMR of crude reaction mixture

Table 3.5

We suspected from previous work that the trifluoroborate was necessary for the reaction to proceed in good yield. With other alkenylboronic acid and pinacolate esters to hand, these were exposed under the same conditions. To our delight, the trifluoroborate gave both an improved selectivity towards transposition and an improved yield (Table 3.6).



Organoboron	Crude ratio ^a		% Yield ^b	
	CA	$\alpha,\beta\text{-O}$	CA	$\alpha,\beta\text{-O}$
$\text{C}_8\text{H}_{17}\text{CH=CHBPin}$	0	0	0	0
$\text{C}_8\text{H}_{17}\text{CH=CHB(OH)}_2$	55	44	8	6
$\text{C}_8\text{H}_{17}\text{CH=CHBF}_3\text{K}$	21	79	11	18

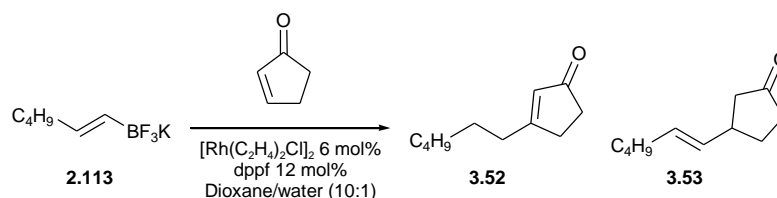
^a determined by ¹H NMR of crude material, ^b isolated yield after flash chromatography

Table 3.6

Owing to the volatility of cyclopentenone and as demonstrated by the isolated yields, the crude ratios are not necessarily a reflection of conversion. Optimisation is required to improve the reaction conversion while still maintaining good selectivity towards transposition.

For the majority of the optimisation process potassium hexenyltrifluoroborate was used in preference to potassium styryl trifluoroborate owing to easier separation of product isomers *via* column chromatography. Catalytic loadings initially remained high as isolated yields were low.

Having determined that the transposition to β,γ -olefin required a higher activation enthalpy than conjugate addition, it is likely α,β -olefin transposition would also have a higher activation enthalpy and therefore require higher temperatures. 80 °C was found to be the optimum temperature for the transposition reaction (Table 3.7). Decreasing the temperature reduced the selectivity, while increasing the temperature created an inseparable mixture of products and increased the formation of side products including homocoupling and protodeboronation.



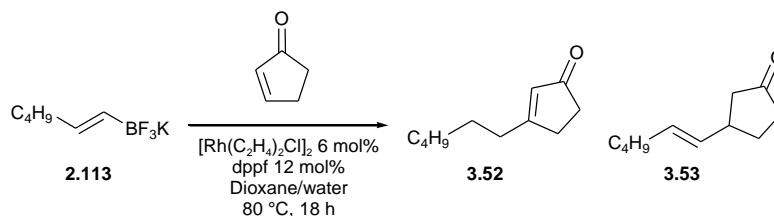
Temp (°C)	α,β -O ^a	CA ^a
60	71	29
80	75	25
100	✓ ^b	✓ ^b

^a determined by ^1H NMR of crude reaction mixture, ^b visible peaks in crude ^1H NMR, but undeterminable integration ratio

Table 3.7

Although the ligand has the most significant effect on transposition, many variables are likely to affect the reaction. Acknowledging the requirement for higher temperatures highlights the need for selective conditions that also minimise protodeboronation to maximise yields.

The solvent system of many rhodium catalysed conjugate additions often includes a minimal amount of water. Water is believed to improve the solubility of potassium trifluoroborate salts and hydrolyses them to the active transmetallating species. Therefore the ratio of dioxane/water was studied and optimised to 1:0.75 (Table 3.8) which improved the selectivity towards α,β -O to 83:17 by ^1H NMR.



Dioxane/H ₂ O	% Product ratio ^a	
	α,β -O	CA
1: 0.1	75	25
1: 0.25	80	20
1: 0.5	81	19
1: 0.75	83	17
1: 1	65	35
0:1	0	0

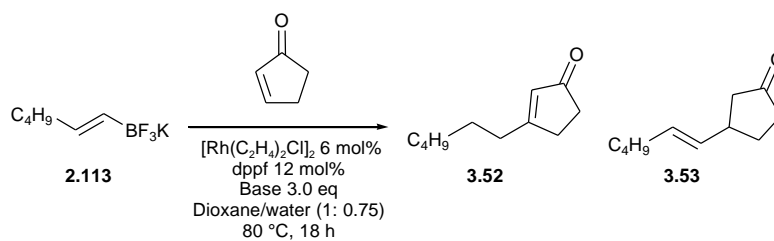
^a determined by ^1H NMR of crude reaction mixture

Table 3.8

Variations in water appear to be crucial in affecting the selectivity. This may be a concentration effect, or it could be a result of the reaction becoming biphasic as the concentration of water increases. An excess of water however shuts down the reaction.

As discussed previously the addition of base can often have a profound effect on the reaction. KOH is a standard base for conjugate addition and as shown by our GC studies, it reduces reaction times for complete conversion. Triethylamine has been shown to generate the more reactive Rh-Et₃N catalytic species to enable room temperature conjugate addition.³ It has also been suggested in some reports that base is required for potassium trifluoroborate hydrolysis.⁴⁸

In the previous work towards lyngbic acid and our GC study, base had an effect on selectivity. Therefore a base screen was carried out using our optimal ratio of dioxane/water and 3.0 equivalents of base (Table 3.9).



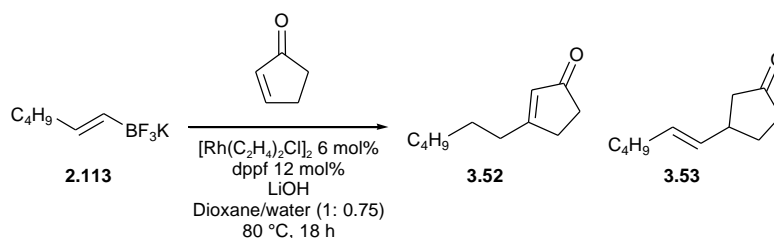
Base (3.0 eq)	% Product ^a	
	$\alpha,\beta\text{-O}$	CA
KOH	93	7
K ₂ CO ₃	72	28
K ₃ PO ₄	94	6
Ba(OH) ₂ ·8H ₂ O	38	61
LiOH	95	5
NaOH	95	5
Et ₃ N	84	16
DIPEA	83	17

^a determined by ¹H NMR of crude reaction mixture

Table 3.9

The base screen revealed that stronger bases increase selectivity towards α,β -olefin transposition. LiOH and NaOH gave optimal results; 95:5 α,β -olefin:conjugate addition (**3.52:3.53**). Also very effective was K_3PO_4 which gave a product distribution of 94:6 in favour of the α,β -olefin. In choosing the desired base, the counter ion effect was considered. From our previous GC studies on the effect of base on conjugate addition and protodeboronation, LiOH and K_3PO_4 were considered optimal as they provided excellent selectivities, but would also facilitate less protodeboronation.

The effect of base concentration was therefore investigated using LiOH and K_3PO_4 . For LiOH, the base concentration was optimised to 5.0 eq, 0.87 M in the optimum dioxane/water ratio (Table 3.10).

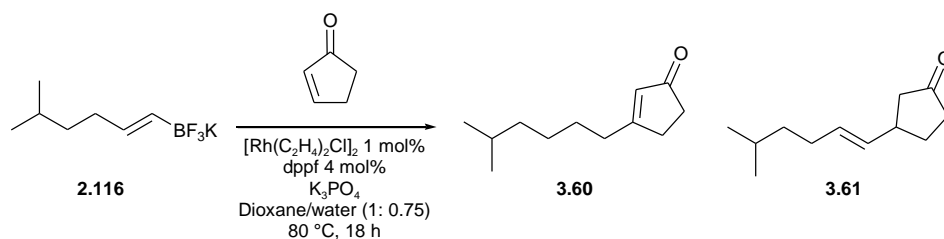


LiOH eq	Conc ⁿ (M)	% Crude Products ^a	
		α,β -O	CA
1	0.17	87	13
2	0.35	89	11
3	0.52	91	9
4	0.70	95	5
5	0.87	99	1
6	1.05	98	2
10	1.74	0	0

^a determined by 1H NMR of crude reaction mixture

Table 3.10

Results in Table 3.11 indicate that 3.0 equivalents of K_3PO_4 is optimal. Selectivity towards α,β -olefin transposition increases as base concentration increases. Above the optimum concentration, excess base causes the reaction to fail, most likely owing to catalyst degradation.



K_3PO_4 (eq)	% Crude Products ^a	
	$\alpha,\beta\text{-O}$	CA
1	65	35
2	61	39
3	67	33
4	59	41

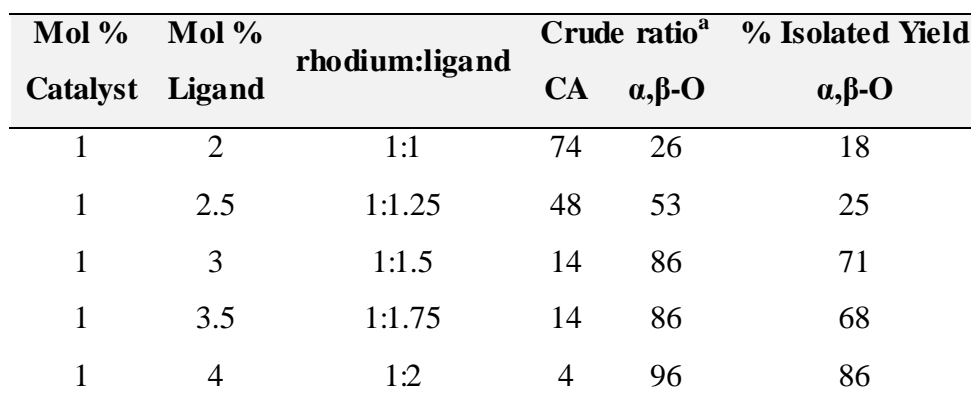
^a determined by ^1H NMR of crude reaction mixture

Table 3.11

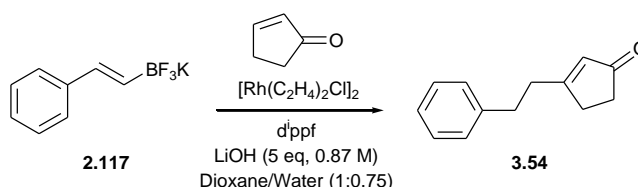
From the studies so far, a very pleasing selectivity of 99:1 $\alpha,\beta\text{-O:CA}$ has been achieved using LiOH. Until this point, few yields had been determined owing to product volatility. Optimum conditions so far are 6 mol% $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$, 12 mol% dppf, 5.0 eq LiOH at 0.87 M in dioxane/water 1:0.75, however, the isolated yield for this reaction was only 53%. This is likely partially owing to product volatility, but also poor conversion as a result of competing protodeboronation.

In order to improve the yield and decrease product volatility, potassium hexenyltrifluoroborate salt (**2.113**) was replaced with potassium styryl trifluoroborate (**2.117**). During the GC studies lower catalytic loadings had facilitated reduced protodeboronation and as such the ligand and catalyst loadings were investigated with the more selective ligand dⁱppf (Table 3.12).

Conversion to $\alpha,\beta\text{-olefin}$ is improved by increasing the ratio of ligand to catalyst. The optimum ratio is 1:4 catalyst to ligand (1:2 [Rh] : bisphosphine). An excess of phosphine ligand is most likely required to prevent catalyst decomposition.

**Table 3.12**

The catalyst loading was reduced to 1 mol% (2 mol% Rh) for the ligand study and after investigating the catalyst loading (Table 3.13) this proved to be optimal. Reducing the catalyst loading not only improves the selectivity, but also dramatically improves the yield. However, reducing the catalyst loading further to 0.5 mol% decreases the selectivity and yield. This can be rationalised alongside the GC results, in that lowering the catalytic loading reduced protodeboronation, increasing the amount of organoboron reagent available for the desired reaction which increases the yield of desired product.



Mol % Cat	Mol % Ligand	Ligand	Ratio ^a		% Isolated Yield
			CA	α,β -O	α,β -O
1	4	DIPPF	4	96	86
2	8	DIPPF	19	81	41
2	8	DPPF	24	76	30
0.5	2	DIPPF	26	74	-

^a determined by ¹H NMR of crude reaction mixture**Table 3.13**

At this point we considered the optimised conditions to achieve α,β -olefin require: enone (1.0 eq), potassium alkenyl trifluoroborate salt (2.0 eq), $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (1 mol%), dⁱppf (or dppf) (4 mol%), LiOH (5eq, 0.87 M) (or K_3PO_4 3.0 eq), dioxane/water (1:0.75).

3.5.7 Aim

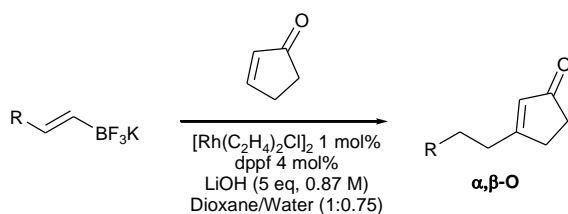
To demonstrate the scope of olefin transposition.

3.5.8 α,β -Olefin Transposition

A number of our potassium alkenyl trifluoroborate salts were reacted with cyclopentenone under our optimised conditions. α,β -Olefin transposition occurred selectively (Table 3.14). Results show that even though dⁱppf is more selective than dppf towards α,β -olefin transposition, dppf affords higher yields of the desired α,β -olefin. Owing to relatively facile separation of α,β -olefin from conjugate addition *via* column chromatography, the higher yielding and less expensive dppf, is the preferential ligand. A minor problem in the isolation of some α,β -olefins was their volatility, or decomposition, for example 3-decyl-cyclopent-2-enone **3.58** was isolated in excellent yield compared to hexyl-cyclopent-2-enone **3.52**.

Internal potassium alkenyl trifluoroborate salts **2.122** and **2.123** were reacted with limited success. Owing to volatility 3-(1-ethyl-butyl)-cyclopent-2-enone **3.66** was afforded in modest yield. However, **3.67**, 3-(1,2-diphenyl-ethyl)-cyclopent-2-enone, was not achieved owing to the steric hindrance of the bulky potassium alkenyl trifluoroborate salt **2.123** and ring constrained cyclopentenone.

Functionalised potassium alkenyl trifluoroborate salts were less compatible under transposition conditions with cyclic enones owing to their propensity to protodeboronate. Since K_3PO_4 demonstrated good selectivity towards transposition and reduced protodeboronation to afford higher yields in the GC study, functionalised potassium alkenyl trifluoroborate salts **2.193** and **2.199** were reacted using K_3PO_4 as base to afford **3.68** and **3.69**, but still in disappointingly low yields. K_3PO_4 could be decreasing protodeboronation by slower hydrolysis and slower release of the transmetallating species, as well as slower catalytic protodeboronation.

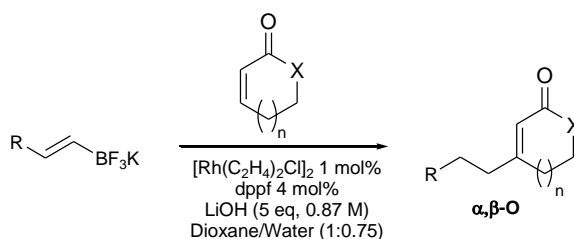


Transposition product	Compound No.	Ligand	Crude ratio CA: α,β -O	% Isolated Yield α,β -O
	3.54	d ⁱ ppf	4:96	86
	3.62	d ⁱ ppf	0	0
	3.62	dppf	68:32	27
	3.60	d ⁱ ppf	1:99	68
	3.60	dppf	10:90	78
	3.63	d ⁱ ppf	0	0
	3.63	dppf	0	0
	3.64	d ⁱ ppf	16:84	27 ^a
	3.64	dppf	37:63	33 ^a
	3.65	dppf	0	0 ^c
	3.52	dppf	0:100	55 ^b
	3.58	dppf	8:92	92
	3.66	dppf	28:72	39 ^b
	3.67	dppf	0	0 ^c
	3.68	dppf	27:73	20 ^d
	3.69	dppf	33:67	34 ^e

^a loss of product possibly *via* ester cleavage, ^b volatile products, evaporation to dryness may have compromised yield, ^c protodeboronation isolated as sole product, ^d 5.0 eq K_3PO_4 , ^e 3.0 eq K_3PO_4

Table 3.14

A range of cyclic α,β -unsaturated carbonyl compounds were exposed under the optimised conditions. α,β -Olefin transposition occurred selectively, but disappointingly in low to modest yields owing to poor conversion (**Table 3.15**). Cycloheptenone was the exception and afforded a low yield of conjugate addition rather than α,β -olefin, likely owing to ring strain or steric bulk preventing transposition. 1-cyclohex-1-enyl-ethanone showed minimal reactivity in the reaction and no desired products were isolated.



Product	Compound No.	Yield (%)
	3.70	36
	3.71	40
	3.72	22
	3.73	49
	3.74	0
	3.75	41

Table 3.15

Darses and co-workers similarly note the poor reaction of 5 and 6 membered cyclic lactones with potassium trifluoroborate salts under rhodium catalysed conjugate addition conditions.³ They postulate this is owing to decomposition of the lactone

through the presence of base and Lewis acidic trivalent fluoroborane in the reaction medium. In comparison with their results the 6 membered lactone similarly yielded greater success. The low yields of these lactones are more likely owing to their lower reactivity, compared to cyclopentenone.

3.5.9 β,γ -Olefin Transposition

Application of the optimised conditions to acyclic monosubstituted activated alkenes is gratifyingly selective for β,γ -olefin transposition. (Table 3.16)

Product	Compound No.	β,γ -O:CA	Yield (%)
	3.36	95:5	89
	3.76	97:3	68
	3.77	77 ^a :11	62
	3.78	88:12	76
	3.79	39:6 ^b	37
	3.80	80:20	46
	3.82	82:18	83

^a 12 % α,β -O also formed, ^b conversion

Table 3.16

The reaction affords good to excellent yields with a range of α,β -unsaturated monosubstituted alkenes. Recently vinylpyridines have been demonstrated as suitable, yet challenging acceptors for rhodium catalysed conjugate addition.¹ Potassium hexenyltrifluoroborate **2.113** reacted successfully with 2-vinyl-pyridine to afford β,γ -olefin **3.80** in a reasonable 46% yield. Contrastingly dimethylitaconate showed poor reactivity and low conversion. The reaction tolerated enantiopure potassium alkenyl trifluoroborate salt **2.193** to successfully afford β,γ -olefin **3.81** with excellent selectivity and yield.

Application of acyclic β -substituted enones under the optimised conditions curiously favoured conjugate addition (Table 3.17). Minimal olefin transposition occurred and conjugate addition products **3.82**, **3.83** and **3.84** were isolated in excellent yield.

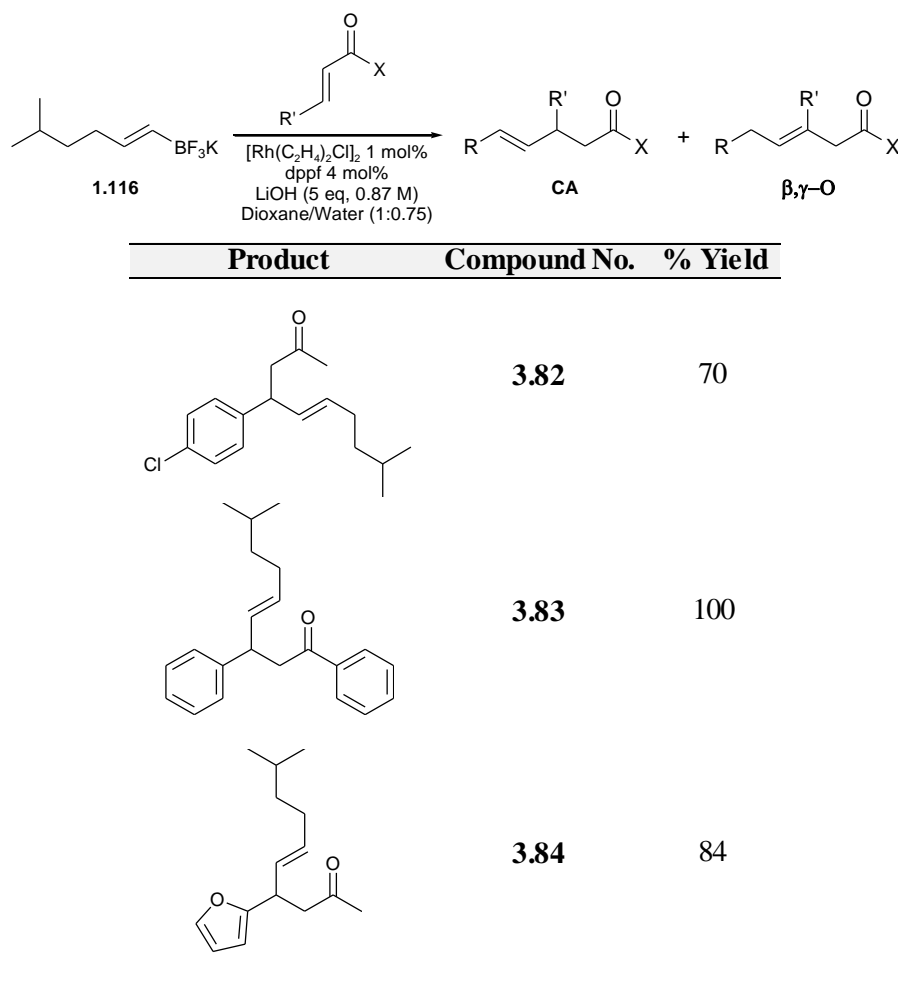
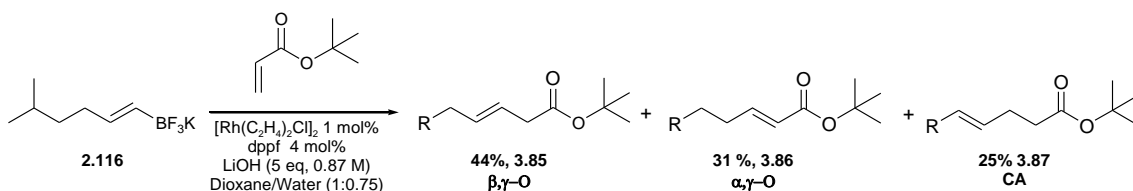


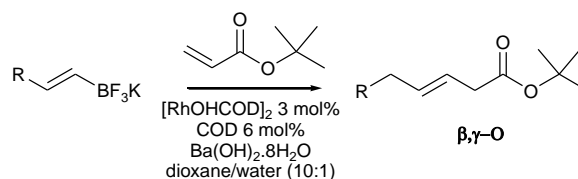
Table 3.17

A further interesting case is *tert*-butylacrylate **3.48**. Under optimised conditions β,γ -olefin **3.85** is the major product within an inseparable mixture of isomers as shown in Scheme 3.20.



Scheme 3.20

In the previous work by Penrose towards lyngbic acid, β,γ -olefin transposition was achieved with *tert*-butylacrylate using cyclooctadiene and $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ as base. Under these conditions a number of potassium alkenyl trifluoroborates undergo highly selective β,γ -olefin addition to *tert*-butylacrylate (Table 3.18).



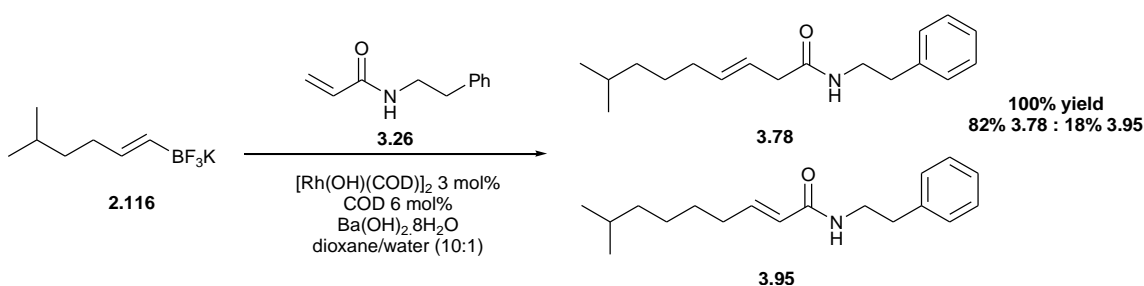
Product	Compound No.	Crude Ratio			% Isolated Yield β,γ -O
		CA	β,γ -O	α,β -O	
	3.85	0	100	0	100
	3.88	9	71	20	60 ^a
	3.89	16	84	0	85
	3.90	7	93	0	93
	3.91	17	67	16	99 ^b
	3.92	42	58	0	36 ^b
	3.93	0	100	0	100
	3.94	0	100	0	98

^a inseparable β,γ -O and α,β -O; ^b all products inseparable

Table 3.18

It is evident these conditions favour β,γ -olefin transposition across a range of alkenyl trifluoroborate salts. Even the sterically hindered internal boronate **2.123**, which was unreactive under α,β -O conditions with cyclopentenone, afforded the desired β,γ -olefin **3.93** in quantitative yield. Presumably the more reactive rhodium-diene complex and less sterically constrained acceptor facilitated the reaction with more challenging substrates.

Application of these conditions to other α,β -unsaturated carbonyl compounds affords conjugate addition, except for *N*-phenethyl-acrylamide **3.26** which afforded an inseparable mixture of β,γ -olefin **3.78** and α,β -olefin **3.95** (82 : 18) in quantitative yield (Scheme 3.21). Therefore the ester and amide functionality appear to innately promote olefin transposition in the presence of $\text{Ba}(\text{OH})_2$.



Scheme 3.21

3.5.10 Conclusions

Potassium alkenyl trifluoroborate salts can be employed in rhodium catalysed additions with a reliable and predictable outcome and the conditions are tunable to favour conjugate addition or olefin transposition. Diene ligands are selective for conjugate addition, while dppf is selective for olefin transposition.

General conditions have been determined to selectively control olefin transposition in the addition of potassium alkenyl trifluoroborate salts to α,β -unsaturated ketones, esters and amides. Cyclic acceptors undergo transposition to α,β -olefins, while acyclic acceptors generally afford β,γ -olefins. β -substituted acyclic acceptors favour conjugate addition.

Extensive studies of the conditions that promote olefin transposition over conjugate addition and protodeboronation have been carried out. The conditions that enable transposition require a delicate balance of additives to do so selectively in high yield.

Ligands appear to be the crucial factor in controlling olefin transposition, however, the return to phosphine ligands increases protodeboronation which has proved a major problem for functionalised potassium alkenyl trifluoroborate salts.

Protodeboronation has been minimised by reducing the catalytic loading as well as selecting the right ligand and base to demonstrate selective addition-olefin transposition of potassium alkenyl trifluoroborate salts to a variety of acceptors.

3.6 Mechanistic Studies

3.6.1 Overview

The mechanism for standard rhodium catalysed conjugate addition is well established. However within the catalytic cycle there are still issues of disagreement; in particular, the precise nature of the organoboron transmetallating species and the mechanism of protodeboronation. As olefin transposition is a new catalytic process, mechanistic experiments are required to determine a plausible mechanism which would explain all our findings. Mechanistic investigation of potassium alkenyl trifluoroborate hydrolysis and protodeboronation is also useful for comparison with current literature regarding potassium aryltrifluoroborates.

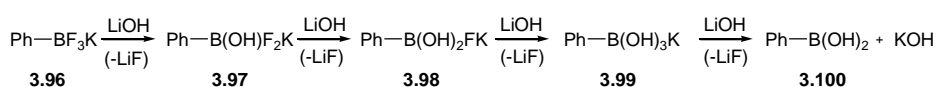
3.6.2 Aims

To investigate potassium alkenyl trifluoroborate hydrolysis, the transmetallating species and the pathway of protodeboronation.

3.6.3 Introduction

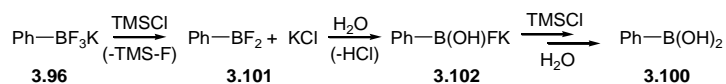
As discussed in chapter 1, potassium trifluoroborate salts have been deprotected to the corresponding boronic acid by a number of fluorophiles. While early claims were made that trifluoroborates have greater nucleophilicity than other organoboron reagents^{49,50} more recent studies by Molander and Batey have determined direct addition of the trifluoroborate is unlikely and that fluoride dissociation or hydrolysis occurs.^{51,52} As such, they have attempted to identify hydrolytic intermediates.

Studies by Molander of ^{19}F NMR indicate not all fluorides are retained on the boron under reaction conditions and the ^{11}B NMR showed signals at 4.35 and 5.47 ppm between those expected for the trifluoroborate and boronic acid.⁵² G  n  t also describes similar ^{19}F and ^{11}B NMR evidence for an $\text{ArBF}_2(\text{OH})\text{K}$ species under their rhodium catalysed conditions with Et_3N . In a study by Yuen, ^{19}F NMR studies also suggested evidence for the intermediates and argued that LiOH was the most effective hydroxide owing to the large lattice enthalpy of formation of lithium fluoride.⁴⁸ Such findings led to conclusions that exchange of fluoride by hydroxyl ions occurs in a mechanism outlined by Yuen (Scheme 3.22). Interestingly, 3.0 equivalents of KHCO_3 revealed slower and incomplete hydrolysis of the potassium phenyltrifluoroborate (**3.96**) to phenyl boronic acid (**3.100**), by ^{19}F NMR.



Scheme 3.22

Vedjes reported the deprotection of trifluoroborates to the difluoroborane **3.101** using anhydrous TMSCl .⁵³ Yuen and co-workers furthered this by reacting difluoroborane **3.101** with water to afford hydroxydifluoroboronate **3.102**. Further equivalents of TMSCl abstract the remaining fluorides which are replaced by water to achieve free boronic acid **3.100** (Scheme 3.23).



Scheme 3.23

Although Molander and Batey were unable to unequivocally prove the transmetallating species, old schools of thought believed from NMR studies and the lack of palladium cross coupling in the absence of base,⁵⁴ that one of the mixed boronate complexes ($\text{RBF}_{3-n}(\text{OH})_n$) was the transmetallating species. This was also argued by Wright *et al.* who determined that reactions have been accelerated by fluoride ions.⁵⁵

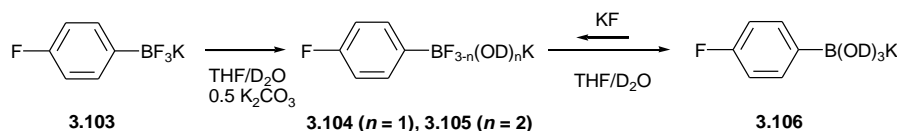
Molander reasoned that since *in situ* hydrolysis of the trifluoroborate to the boronic acid occurs during the reaction and boronic acids have been applied successfully in similar yields, the boronic acid could equally be the transmetallating species.⁵⁶

In 2010 an excellent study of the roles of boronic acid and fluoride in the Suzuki-Miyaura reaction was presented by Lloyd-Jones and co-workers.⁵⁷ Their thorough

investigations provided great insight into trifluoroborate hydrolysis and the transmetallating species.

Although their investigations involve arylboronates and a palladium cross coupling, the concepts are likely to be transferable to potassium alkenyl trifluoroborates and rhodium catalysed conditions.

Potassium trifluoroborates are hydrolysed to boronic acids under reaction conditions as confirmed by ^{19}F NMR analysis (Scheme 3.24). The mixed species, $[\text{ArBF}_2(\text{OD})]^- \text{K}^+$ was only detected at high water concentrations where it existed in rapid equilibrium with boronate **3.106** and KF. The equilibrium is driven to the boronic acid by base, glassware and fluoride sequestration. Reversible generation of the trifluoroborate is possible, but it is not in equilibrium with the mixed boronate. Also, as the concentration of water was increased, the formation of trihydroxyborate **3.106** was increased (Scheme 3.24).



Scheme 3.24

The transmetallation of $[\text{PhBX}_3]^-$ ($\text{X} = \text{OH}, \text{F}$) to $[\text{Pd}(\text{Br})\text{Ar}(\text{L})_n]$ ($\text{L} = \text{PPh}_3$; $n = 1, 2$) in THF was studied. The energy barrier to transmetallation decreases as the ligation of boron by fluoride decreases. The trifluoroborate has a decreased ability to complex to palladium and the phenyl moiety has reduced nucleophilicity. They also conducted deuterium isotope studies using mixtures of deuterium labelled aryltrifluoroborate salts and boronic acids. The product indicated greater deuterium incorporation from the boronic acid. Therefore the dominant transmetallating species is boronic acid rather than a mixed borate. This confirmed the conclusion that potassium trifluoroborates serve as a reservoir for boronic acids.

Potassium trifluoroborates have been more efficient in some reactions compared to boronic acids. Lloyd-Jones suggests the efficiency is in reduced side products rather than an effect on the rate of reaction; catalytic turnover can be limited by slow and variable rates of hydrolysis. Under their palladium catalysed conditions, in aqueous THF, protodeboronation was negligible and homocoupling a greater problem, but both are suppressed when the boronic acid is generated *in situ*.

In contrast to this result, under rhodium catalysis more side products occur when the boronic acid is generated *in situ* from the trifluoroborate. This is most likely owing to more facile protodeboronation of the mixed alkenylboronate.

Fluoride can catalyse hydrolytic reduction of the precatalyst $[\text{PdCl}_2(\text{PPh}_3)_2]$ *via* phosphorane **3.107** (Figure 3.2) in $\text{THF}/^{18}\text{OH}_2$. This catalyst activation leads to the formation of $\text{PPh}_3=^{18}\text{O}$ detected by ^{31}P NMR analysis.

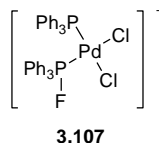


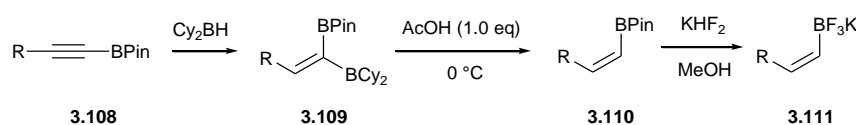
Figure 3.2

This could explain the requirement for excess phosphine ligand in the rhodium catalysed reaction.

3.6.4 Protodeboronation

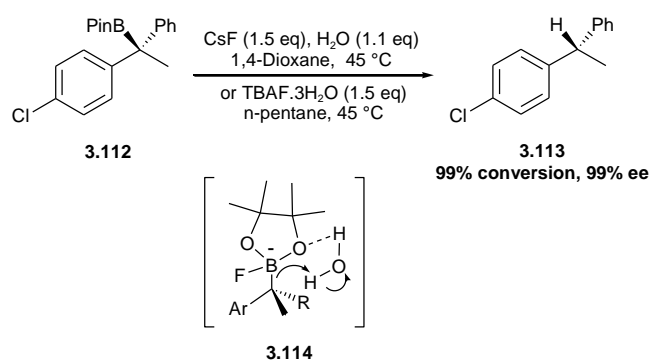
In recent literature there is often disagreement about whether the mechanism of protodeboronation occurs *via* hydrolysis or transition metal catalysis.

Selective protodeboronation has been employed in the synthesis of *cis*-alkenyl trifluoroborates **3.111** as part of a hydroboration-protodeboronation synthesis.⁵⁸ The difference in reactivity between pinacolboronic esters and dialkylboranes has been utilised by selecting 1.0 equivalent acetic acid as an appropriate protonating agent to achieve chemoselective protodeboronation (Scheme 3.25).



Scheme 3.25

More recently, Aggarwal reported protodeboronation of tertiary boronic esters in the synthesis of enantioenriched tertiary alkanes (Scheme 3.26).⁵⁹ Alkylboronic esters had previously been reported as stable to acids and bases, but protodeboronation of catecholboronic esters had been reported in the presence of methanol.^{60, 61} Fluoride sources CsF and TBAF enabled successful protodeboronation. This was explained by the reaction occurring *via* boronate **3.114** as the formation of B-F (613 kJ/mol) is a greater driving force than B-O (536 kJ/mol).



Scheme 3.26

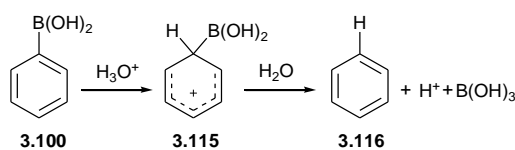
Solutions to minimise protodeboronation have involved using large excesses of organoboron reagents,⁶² switching to MIDA, DAN, triol or trifluoroborates which slowly hydrolyse to the boronic acid. Lloyd-Jones and co-workers have determined that since the boronic acid and trihydroxyborate exist in rapid equilibrium, a decrease in the concentration of D₂O (in a D₂O/THF mixture) shifted the equilibrium from >98% boronate to >98% boronic acid which suppressed protodeboronation, indicating protodeboronation occurs more rapidly through the boronate.⁵⁷ The high concentration of water in the rhodium catalysed transposition reaction could shift the equilibrium towards the boronate which facilitates protodeboronation.

During the hydrolysis of potassium trifluoroborates with aqueous base to boronate **3.106** they reported protodeboronation was faster at 55 °C than at room temperature. It is interesting to note that under Molander's hydrolysis conditions using aqueous silica gel, protodeboronation was also observed at higher temperatures (50 °C).⁶³ Our work is in agreement with this; protodeboronation occurs more rapidly at higher temperatures.

Previous kinetic investigations of the protodeboronation of arylboronic acids have revealed four types of mechanisms can occur: acid catalysis, hydroxide ion catalysis, solvent reaction and metal catalysis.⁶⁴

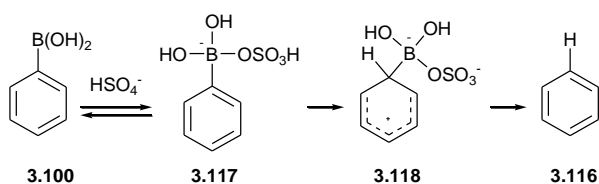
General acid catalysed mechanisms involve proton transfer from acid to the borylated carbon.⁶⁵ In acidic solutions the activation energy ranged from 15 to 24 kJmol⁻¹, increasing as acidity decreased. The rate of protodeboronation was highly sensitive to substrate substituents, indicating three possible proton transfer mechanisms are possible

depending on substrate and acidity. The simplest mechanism is described as an S_E2 reaction whereby proton transfer occurs from the hydronium ion (Scheme 3.27).



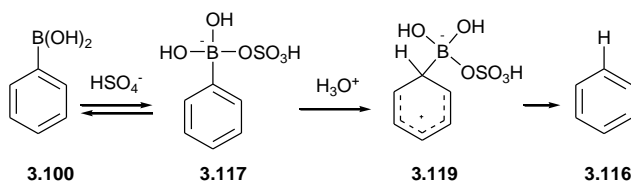
Scheme 3.27

They also discuss how the boronate intermediate can facilitate protodeboronation under acidic conditions (Scheme 3.28). Firstly by inductive effects; the negatively charged boron increases the susceptibility for electrophilic attack on the adjacent carbon. Secondly, by increasing the ability for proton transfer *via* a 6-membered transition state.



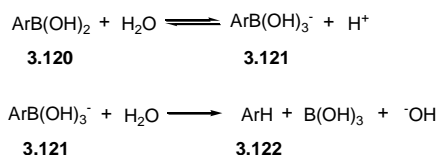
Scheme 3.28

Further to this mechanism is the possibility of protonation of boronate **3.117** by a hydronium ion (Scheme 3.29).



Scheme 3.29

A second type of general mechanism is believed to be hydroxide ion catalysis and involves proton transfer from water to the boronate anion **3.121** (Scheme 3.30).⁶⁶ An increase in base concentration only increases the rate of protodeboronation when boronate anion concentration increases.

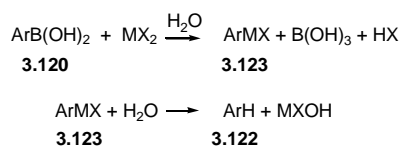


Scheme 3.30

The third mechanism is independent of pH and occurs through a solvent hydronium ion reacting with a boronate anion, in a similar mechanism to Scheme 3.30.

Finally an alternative mechanism to protodeboronation *via* metal catalysis has also been reported (Scheme 3.31).⁶⁴ Metallic salts of copper, lead, silver, cadmium, zinc, cobalt,

magnesium, nickel, palladium and gold can catalyse protodeboronation. Transmetallation of the boronic acid leads to the arylmetal species **3.123**. Proton transfer may then take place from a water molecule, either in solvent or as a ligand.



Scheme 3.31

Under olefin transposition conditions, protodeboronation of alkenyl trifluoroborates is likely to occur under a combination of mechanisms. Hydroxide ion catalysis or solvent reaction occurs with the trihydroxy or mixed borate while metal catalysed protodeboronation of the boronic acid is also possible.

3.6.5 Hydrolysis and protodeboronation studies of potassium alkenyl trifluoroborates

Alkenylboronic acid **3.124** was exposed to increasing equivalents of LiOH in D₂O to gradually form boronate anion **3.125**. The reaction was followed by ¹¹B NMR and mass spectrometry. As shown in Figure 3.3 the majority of the boronic acid **3.124** (28.48 ppm) initially existed as the more stable boroxine such as **3.126** (20.07 ppm). This was confirmed by mass spec analysis which showed the presence of dimers ([M-H]⁺ = 277.0720), trimers ([M-H]⁺ = 407.1098) and tetramers ([M-H]⁺ = 537.1489). As increasing equivalents of LiOH were added the polymeric species are broken apart to form boronate **3.125** (2.32 ppm).

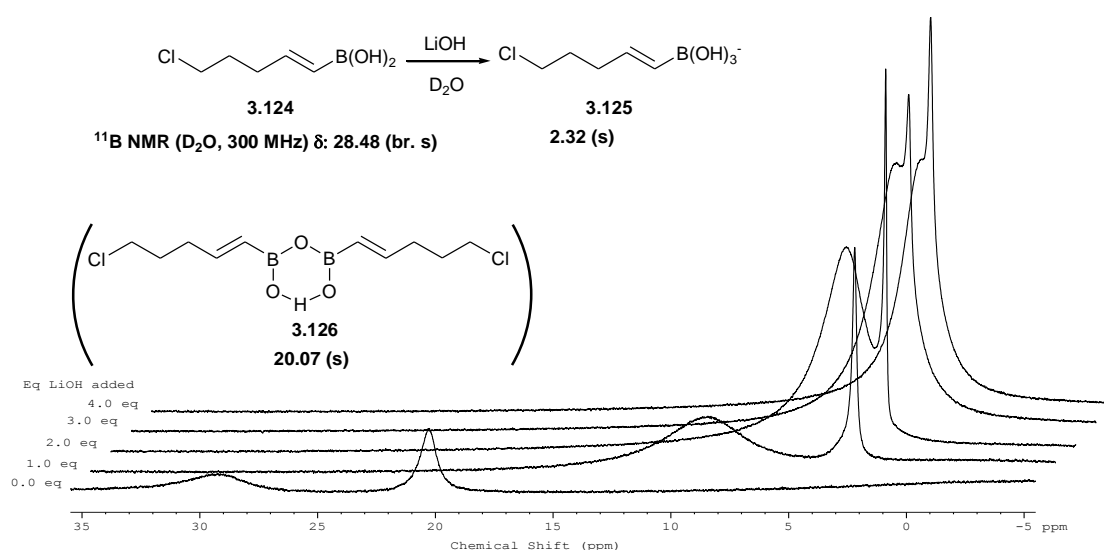


Figure 3.3

These results are as expected from similar studies with arylboronic acids. Considering this, it is reasonable to assume that potassium alkenyl trifluoroborate salts hydrolyse to the boronate in a similar fashion to potassium aryl trifluoroborate salts. Lloyd-Jones had reported that unsurprisingly 3.0 equivalents of base are required for complete hydrolysis and F-OH exchange to afford the trihydroxyborate. They observed time averaged peaks for mixed boronates until hydrolysis was complete. Therefore several alkenylpotassium trifluoroborate salts were exposed to 3.0 eq LiOH in dioxane/D₂O (1:0.75, 0.35 M) and their hydrolysis followed over time by ¹¹B NMR at room temperature.

Figure 3.4 shows that in the presence of 3.0 eq LiOH, potassium hexenyl trifluoroborate **2.113** slowly hydrolyses to the trihydroxyborate **3.128**, with minimal boronic acid **3.127** present. At room temperature, hydrolysis is slow and the boronic acid-borate equilibrium favours the borate thereby releasing boronic acid slowly into the reaction. Slow release of the boronic acid leads to minimal protodeboronation and hence this particular substrate gives good yields in the transposition reactions.

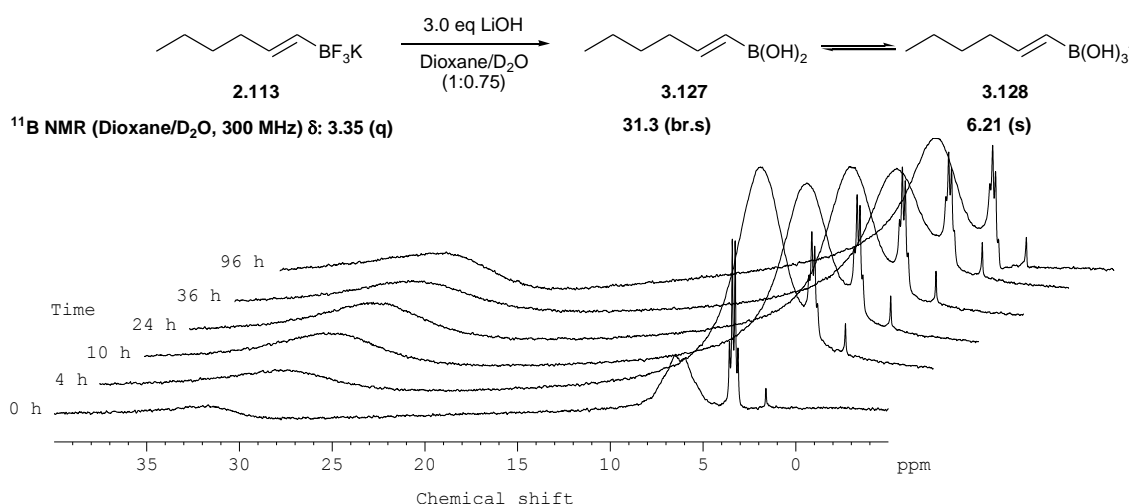


Figure 3.4

Potassium 5-chloropentenyltrifluoroborate **2.115** hydrolyses more slowly than potassium hexenyltrifluoroborate **2.113** (Figure 3.5). The boronic acid-boronate equilibrium still favours the boronate, but to less extent. A faster release of boronic acid could explain the low yields of this substrate in the transposition reaction with the less reactive rhodium-phosphine catalyst since rhodium catalysed protodeboronation is more facile than the desired addition reaction under these conditions.

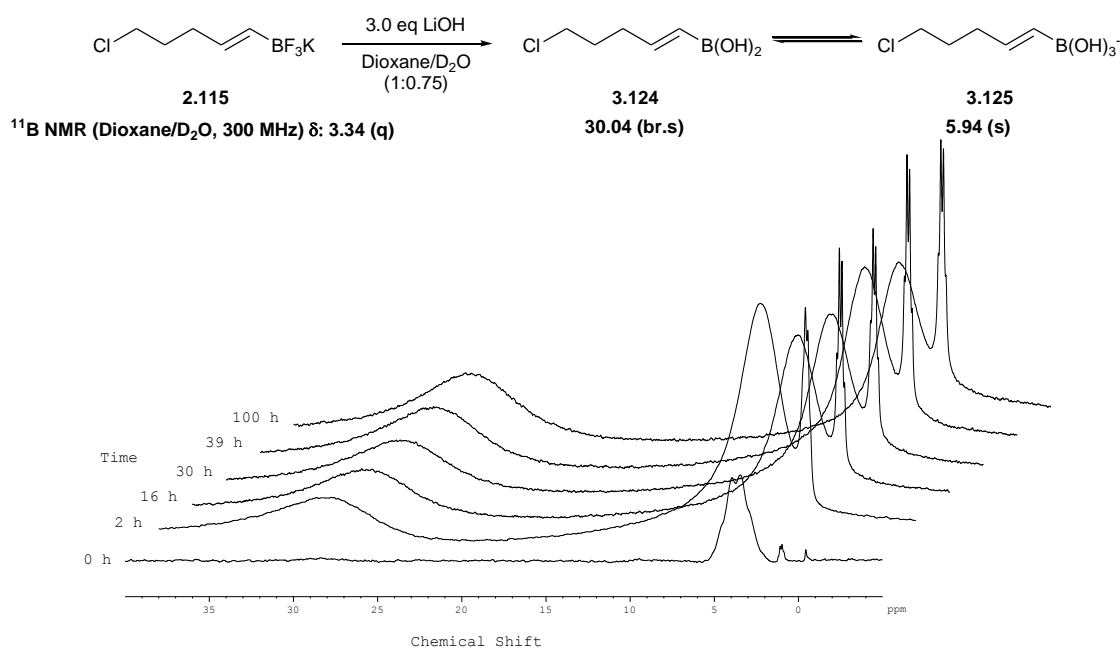


Figure 3.5

Potassium alkenyl trifluoroborate salt **2.120** is more rapidly hydrolysed to the boronate (Figure 3.6). The boronic acid-boronate equilibrium favours the boronic acid, so much so boroxines form (^{11}B NMR δ : 19.49). More rapid release of boronic acid could lead to increased metal catalysed protodeboronation thereby affording low yields of this substrate and similar substrates in the transposition reaction.

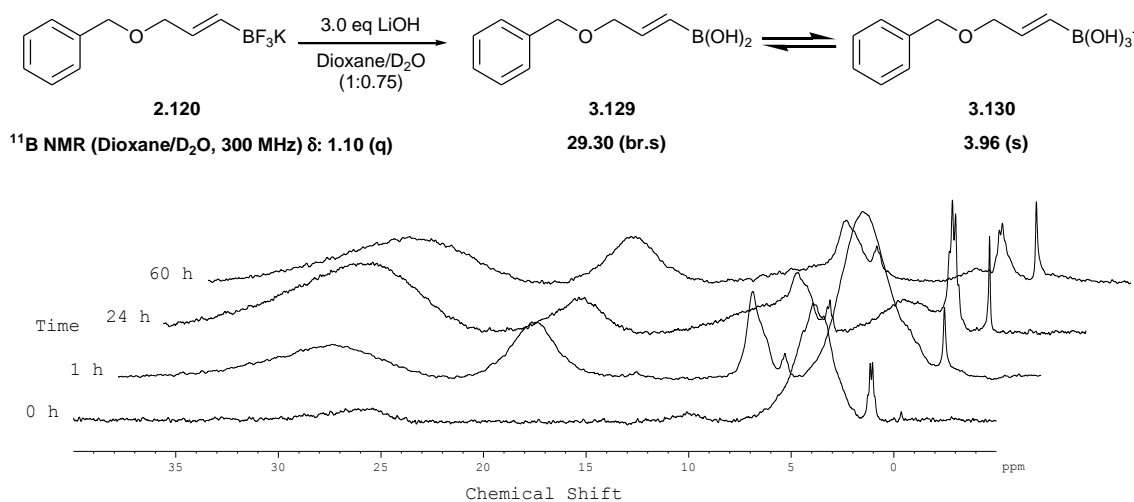
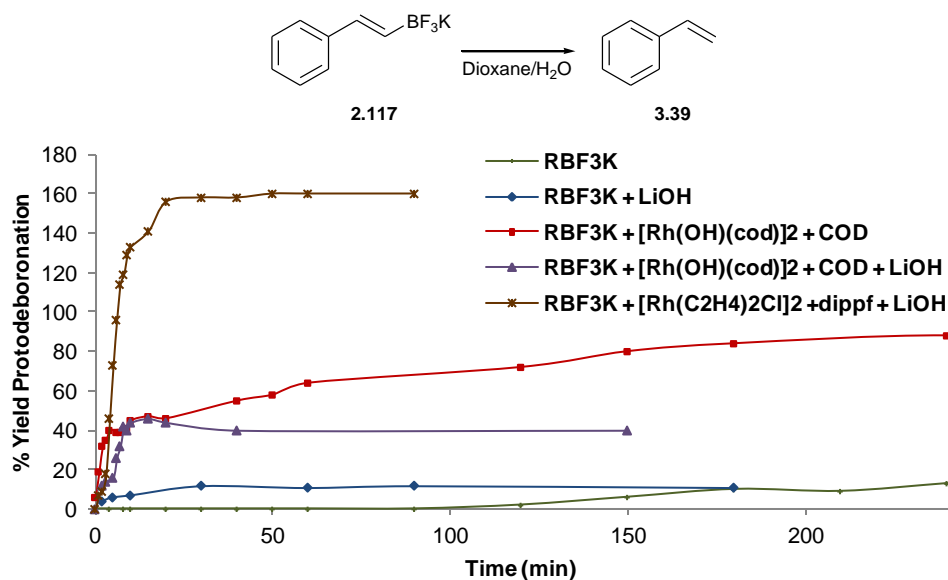


Figure 3.6

Protodeboronation can occur under a variety of mechanisms. In transition metal catalysis, in particular using rhodium it is unclear whether the major pathway of protodeboronation, is base or metal catalysed. Therefore, potassium styryl

trifluoroborate salt **2.117** was exposed to the typical GC reaction conditions in the absence of MVK to focus directly on protodeboronation. Graph 3.16 highlights formation of protodeboronation with and without rhodium, the effect of base and the remarkable ligand effect.

Protodeboronation of potassium styryltrifluoroborate



Graph 3.16

The results shown in Graph 3.16 indicate protodeboronation under the reaction conditions is predominantly a metal mediated process, but basic and solvent mechanisms also occur slowly throughout the reaction.

In the absence of rhodium and base, no protodeboronation occurs in the first 2 hours. With the addition of base, protodeboronation starts to occur slowly after several minutes. In the presence of [Rh(OH)(cod)]₂ protodeboronation occurs more rapidly, but appears to be suppressed by the addition of base. This could be owing to base favouring the trihydroxyborate over boronic acid and hence slowing transmetallation, or it could be base restricting protonation of the transmetallated species.

The most crucial result was obtained using phosphine ligand dⁱppf which dramatically increased the rate of protodeboronation, compared to diene ligands. This demonstrates the balance of our problem; whilst phosphine ligands such as dⁱppf are selective for transposition, they also facilitate faster protodeboronation. This is unfortunate since some, particularly more functionalised alkenylboronates are sensitive to protodeboronation, through faster release of the boronic acid, but also since

alkenylboronates are probably least stable to protodeboronation compared to alkyl and aryl boronates.^{67,68}

3.6.6 Conclusions

Hydrolysis of potassium alkenyl trifluoroborates occurs *via* mixed boronate species to boronic acids which are in equilibrium with trihydroxyboronates. Base is not required, but does increase the rate of hydrolysis and pushes the equilibrium towards trihydroxyboronates. Boronic acids are the most likely transmetallating species and are slowly released through the use of the potassium trifluoroborates.

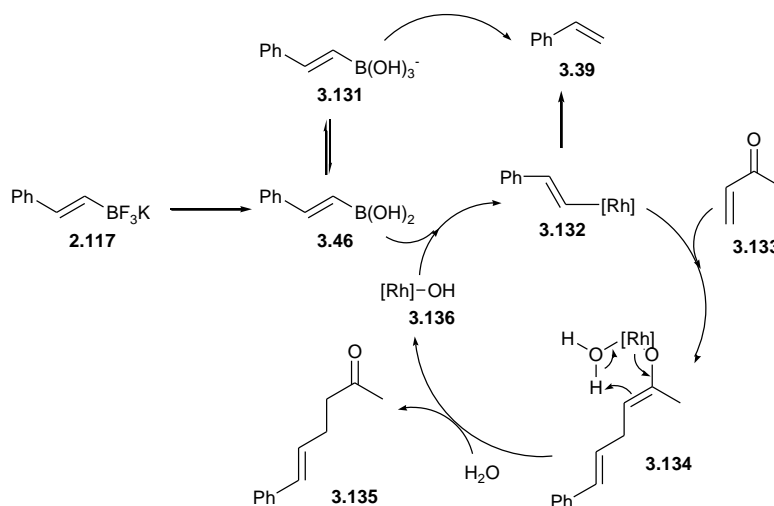
In the olefin transposition reaction the major mechanism of protodeboronation is rhodium catalysed, which unfortunately is greatly influenced by phosphine ligands. Protodeboronation also occurs slowly *via* hydrolysis in aqueous and basic solutions, through the trihydroxyborate, or as highlighted through Aggarwal's work, through a mixed boronate.

3.6.7 Aims

To investigate the mechanism of olefin transposition and propose a catalytic cycle to account for α,β -olefin and β,γ -olefin selectivity

3.6.8 Mechanism of Conjugate addition

Hayashi *et al.* reported a detailed mechanistic study of rhodium catalysed conjugate addition in 2002.⁶⁹ Scheme 3.32 depicts the standard catalytic cycle. The first step of the catalytic cycle requires transmetallation of the organoboronic acid **3.46** to the active rhodium-hydroxyl species **3.136** to form **3.132**. This is followed by co-ordination and carbometallation of the α,β -unsaturated ketone to form **3.134**. Hydrolysis of the rhodium enolate **3.134** eliminates conjugate addition product **3.135** to successfully regenerate the active rhodium-hydroxy catalyst **3.136**.

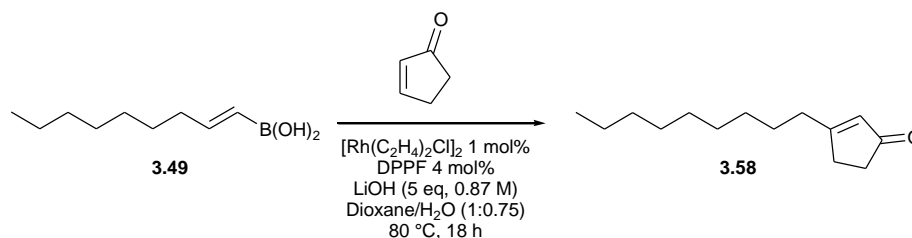


Scheme 3.32

More recently Hayashi *et al.* also reported that in anhydrous reactions the boron species eliminated after transmetallation can act as a Lewis acid and transmetallate the rhodium-enolate.⁷⁰ The α -position is deuterated upon quenching the reaction with d_4 -acetic acid.

3.6.9 Olefin transposition mechanistic studies

In early experiments potassium trifluoroborates afforded higher yields than boronic acids in the olefin transposition reaction. Given that the boronic acid is the transmetallating species, this can be explained mechanistically by facile protodeboronation, especially since the organoboron is stirred with rhodium at room temperature for 15 min prior to addition of the enone. To investigate whether the potassium trifluoroborate just enables slow release of boronic acid or if F^- has any influence in the reaction, boronic acid was added slowly over the course of the reaction. Decenylboronic acid **3.49** was dissolved in the minimal anhydrous dioxane (0.1 mL) and added *via* syringe over the course of the reaction (Scheme 3.33).



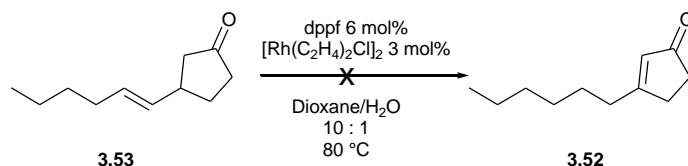
Scheme 3.33

Satisfactorily, the desired α,β -olefin was isolated in identical yield to that obtained using the corresponding potassium alkenyl trifluoroborate salt in one portion at the start of the reaction. Thus indicating the benefit of the trifluoroborate in the reaction is to provide a slow release of boronic acid.

The initial steps in the mechanism using potassium alkenyl trifluoroborates are as those for conjugate addition (Scheme 3.32). The potassium trifluoroborate **2.117** is hydrolysed to boronic acid **3.46** which can be transmetallated to form alkenylrhodium species **3.132**. The boronic acid is also in equilibrium with the trihydroxyborate **3.131**. Protodeboronation can occur *via* the alkenyl-rhodium species and the trihydroxyborate as discussed previously.

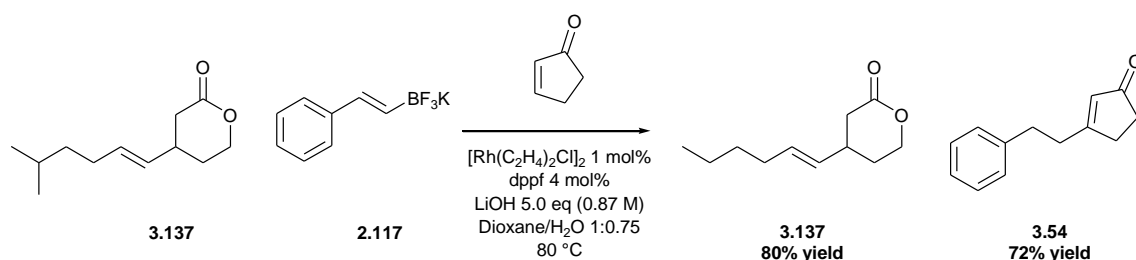
As olefin transposition is a new reaction, several experiments were undertaken to investigate whether the mechanism was simply isomerisation of the conjugate addition product, or if it is completed by an entirely different pathway.

Exposure of conjugate addition product to transposition conditions generated no transposed product (Scheme 3.34). The conjugate addition adduct was quantitatively recovered. Addition of 0.1 eq Schwartz reagent or Et_3SiH also afforded no α,β -olefin.



Scheme 3.34

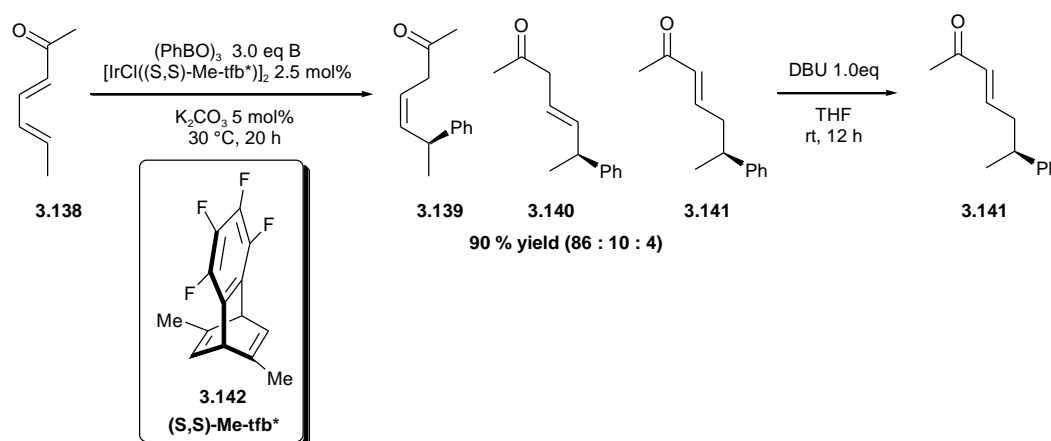
A cross over experiment was also conducted by adding conjugate addition product **3.137** to a new reaction with a different enone and potassium trifluoroborate salt (Scheme 3.35). The conjugate addition product **3.137** was recovered and the new α,β -olefin **3.54** isolated. No mixed products were observed or isolated.



Scheme 3.35

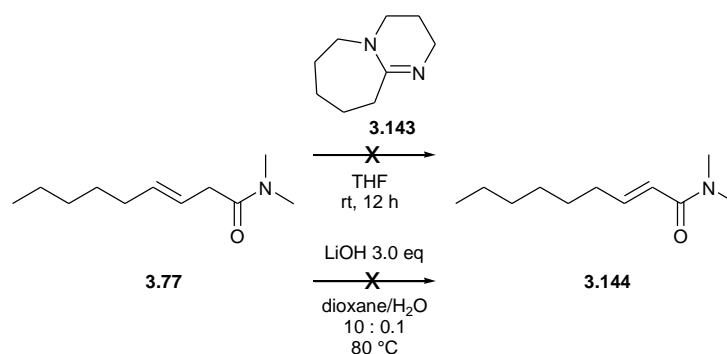
These results suggest that once conjugate addition product is formed it does not undergo isomerisation and therefore a different rhodium catalysed mechanism must be predominantly occurring to generate olefin transposition products.

In an interesting report by Hayashi, an iridium catalysed 1,6-addition to $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compound **3.138** afforded mixtures of α,β and β,γ olefins **3.141**, **3.139** and conjugate addition **3.141** (Scheme 3.36).⁷¹ Isomerisation to the α,β -olefin **3.142** was completed by exposing the mixture to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).



Scheme 3.36

Therefore synthesised β,γ -olefin **3.77** was reacted with DBU **3.143**, and LiOH but no isomerisation to the α,β -olefin **3.144** took place and starting materials were recovered quantitatively. Since this example favours olefin transposition within the reaction and yet is difficult to enolise it suggests the ‘isomerisation’ is likely to be a rhodium catalysed, rather than base mediated process (Scheme 3.37).

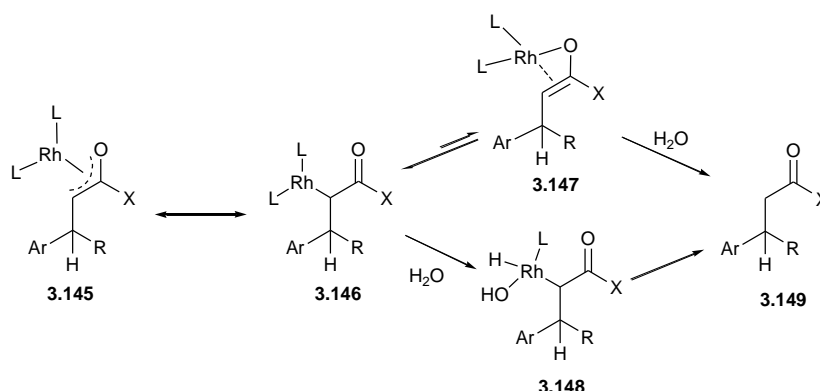


Scheme 3.37

It is likely the pathway for olefin transposition follows the same pathway as conjugate addition until formation of the rhodium enolate. In our proposed mechanism the fate of the rhodium enolate determines whether conjugate addition or transposition occurs.

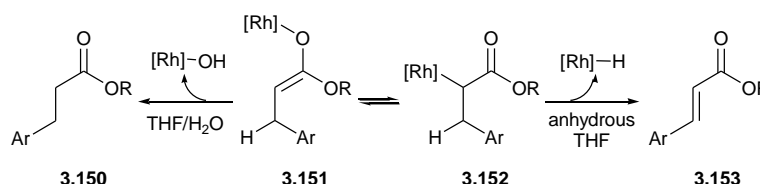
Hayashi observed the oxa- π -allyl structure is adopted in preference to the rhodium enolate. Bergman and Heathcock reported some oxygen-bound rhodium enolates.⁷² However the Rh-C tautomer **3.148** is favoured over the Rh-O enolate **3.147** owing to the soft nature of rhodium.^{73,74}

Hydrolysis of the rhodium oxa- π -allyl species is required to obtain conjugate addition product and can occur through the Rh-C or Rh-O bond (Scheme 3.38). Hydrolysis of the Rh-C bond is an oxidative addition-reductive elimination pathway with water rather than direct hydrolysis as a carbanion and is highly dependent on the ligand.⁷⁵



Scheme 3.38

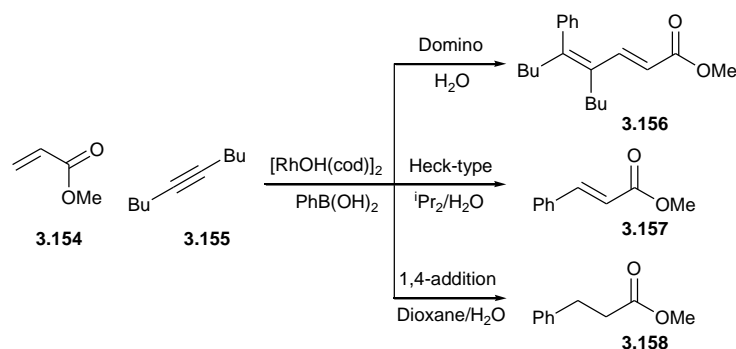
Alternatively β -hydride elimination of the rhodium oxa- π -allyl species could occur as in Heck couplings. We believe this is the crucial step for olefin transposition. Interestingly in typical palladium catalysed Heck reactions dppf has been used with great success as a selective ligand and is often more selective than dppf.⁷⁶ The first rhodium catalysed Heck coupling was reported by Lautens *et al.*⁷⁷ followed by Genêt *et al.*⁷⁸ and Mori *et al.*⁷⁹ In a number of early rhodium catalysed Heck-type reactions the selectivity was reported to be highly solvent dependent.⁸⁰ In protic media, such as THF/H₂O, hydrolysis was faster than β -hydride elimination, whereas under anhydrous conditions enolate hydrolysis cannot occur and instead β -hydride elimination affords the Heck product **3.153** and a rhodium-hydride species (Scheme 3.39).⁷⁹



Scheme 3.39

The key to controlling the selectivity of olefin transposition over conjugate addition therefore lies in promoting β -hydride elimination over hydrolysis.

In more recent years, conditions have been developed to tune towards β -hydride elimination of α -rhodium carbonyls in the presence of water.^{81,82} An interesting and relevant example is a rhodium catalysed intermolecular carbometalation/Heck-type coupling in water (Scheme 3.40). Solvent effects were key in changing the reaction selectivity towards different products. In wet organic solvents, such as dioxane or THF, conjugate addition **3.158** was the major product, while in a biphasic system of $i\text{Pr}_2\text{O}/\text{H}_2\text{O}$ the Heck-type adduct **3.157** was favoured. In aqueous media however, a three component coupling occurred to predominantly achieve 1,3-diene **3.156**. They propose addition of the alkyne **3.155** to the acrylate **3.154** and addition of the boronic acid to the alkyne in either a stepwise or concerted fashion, followed by β -hydride elimination. They were unable to explain the role of water and why β -hydride elimination was favoured over hydrolysis under these conditions.



Scheme 3.40

It should come as no surprise therefore that the ratio of dioxane/ H_2O influenced olefin transposition selectivity, albeit only mildly.

In 2007, Zou and co-workers reported a detailed investigation of competing rhodium-phosphine catalysed conjugate addition and Heck-type coupling in a biphasic toluene/ H_2O system.⁸³ They determined that the phosphine ligand, the ratio of boronic acid to α,β -unsaturated carbonyl and the pH value of the aqueous phase significantly affected the competition. Basic conditions were essential to favour β -hydride elimination. Excess boronic acid favoured conjugate addition, while excess olefin favoured Heck-type coupling. Higher temperatures also favoured β -hydride elimination. In a 1,2 addition, β -hydride elimination has also been shown to be more competitive at higher temperatures (100 °C cf. 70 °C).⁸⁴

The rhodium environment is crucial in determining the propensity for hydrolysis or β -hydride elimination and is highly influenced by ligands. β -hydride elimination of the α -rhodium species requires an open coordination site on rhodium, therefore bidentate ligands would typically disfavour this. Interestingly in Zou's study, PPh_3 favoured β -hydride elimination while large bite angle diphosphine ligands such as dppf favoured conjugate addition. Smaller diphosphine ligand bite angles ($<90^\circ$) had greater selectivity towards β -hydride elimination. High ligand to catalyst loadings (10 mol% L: 3 mol% Rh) increased the rates and yields of reactions.

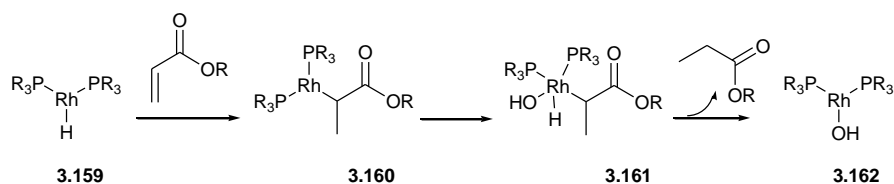
The selectivity was also affected by bidentate ligand rigidity. Lautens and co-workers have also reported that steric effects of ligands impact the selectivity of conjugate addition vs. Heck coupling in emulsion systems.⁸⁵ Sterically-hindered ligands such as *tert*-butyl-amphos were highly selective towards β -hydride elimination.

In a recent addition of aryl boronates to α -acetamidoacrylic esters, conjugate addition was competing with a Mizoroki-Heck type pathway. Norbornadiene and ethene ligands favoured the Heck product in dioxane/water.⁸⁶

Also evident from each of these studies was that carbonyl structures also significantly affect β -hydride elimination, which increases as the substrates carbonyl becomes more electron rich. For example, MVK selectively gave conjugate addition, whereas unsaturated amide gave a mixture and unsaturated esters preferentially gave Heck product.

Lautens and co-workers similarly reported *tert*-butylacrylate was selective for β -hydride elimination while acrylamides facilitated double β -arylation.⁸⁵ Interestingly, sterically bulky boronic acids such as 2,6-dimethylphenylboronic acid prevented β -hydride elimination.

β -hydride elimination results in a rhodium hydride which needs to be transformed into the rhodium hydroxyl species for the catalytic cycle to continue. The rhodium hydride can either be hydrolysed⁸⁶ to form dihydrogen and Rh-OH or it can reduce excess olefin in order to regenerate Rh-OH as indicated in Scheme 3.41.⁸⁷ This explains why excess acrylate promotes β -hydride elimination as it acts as a sacrificial hydride acceptor to turn over the catalytic cycle.



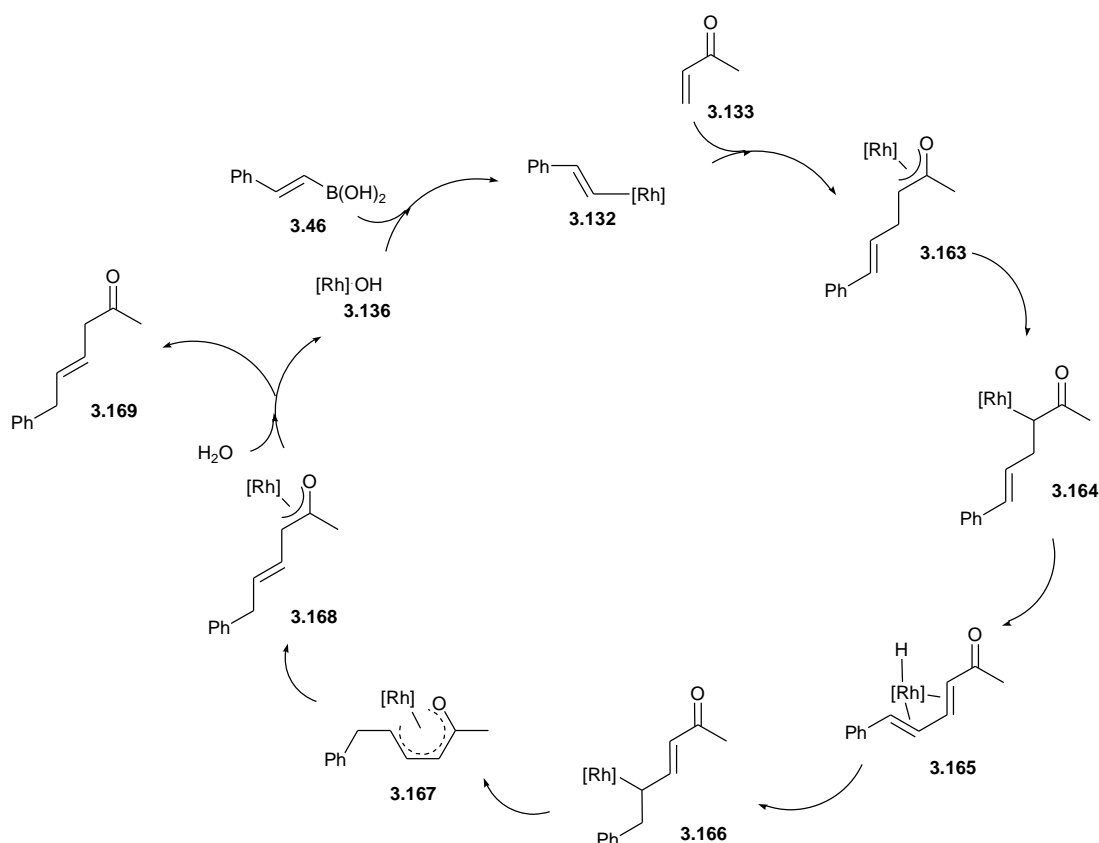
Scheme 3.41

Rh-H hydrolysis has been reported as an equilibrium in water, but it has been observed as a slower pathway than alkene reduction in reactions.⁸⁸ It would therefore seem likely that where possible an internal reaction with the generated Rh-H would be more preferable.⁷⁵ This is encouraging for the proposed mechanism of olefin transposition.

3.6.10 Proposed mechanism for olefin transposition

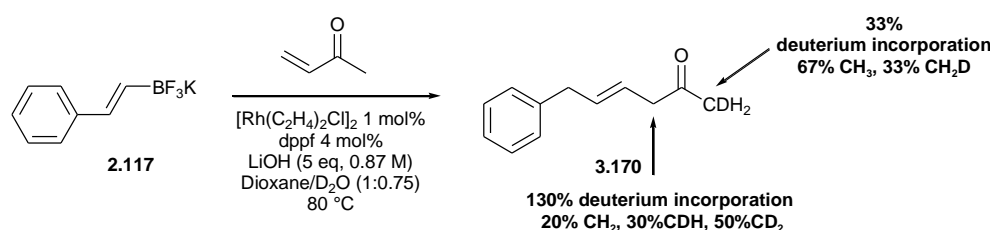
Scheme 3.42 details the proposed mechanism for β,γ -olefin transposition with acyclic α,β -unsaturated carbonyls under the optimised conditions. As discussed the catalytic cycle is likely to begin with transmetalation of the alkenylboronic acid **3.46** followed by co-ordination and carbometallation of MVK (**3.133**) to form the oxa- π -allyl species **3.163**. The ligand and base then promote β -hydride elimination over hydrolysis leading to species **3.165**, a stabilised rhodium-hydride intermediate. Based on our cross over experiment, the rhodium-hydride undergoes an intramolecular not intermolecular reaction. It is worth noting that the hydride additives had no effect on the reaction, presumably as the rhodium-hydride would not be able to complete the necessary 1,6-hydride addition if β -hydride elimination had not taken place.

From the $\alpha,\beta,\gamma,\delta$ -unsaturated intermediate **3.165**, a 1,6-hydride addition could afford **3.166** which is followed by isomerisation to afford the more thermodynamically stable oxa- π -allyl species **3.168**. In 1,6-additions of linear $\alpha,\beta,\gamma,\delta$ -unsaturated substrates the oxo- π -pentadienyl-Rh(I) complex **3.167** has been suggested.⁸⁹ Hydrolysis by α -protonation occurs to eliminate β,γ -olefin **3.169** and regenerate the active rhodium-hydroxy species.



Scheme 3.42

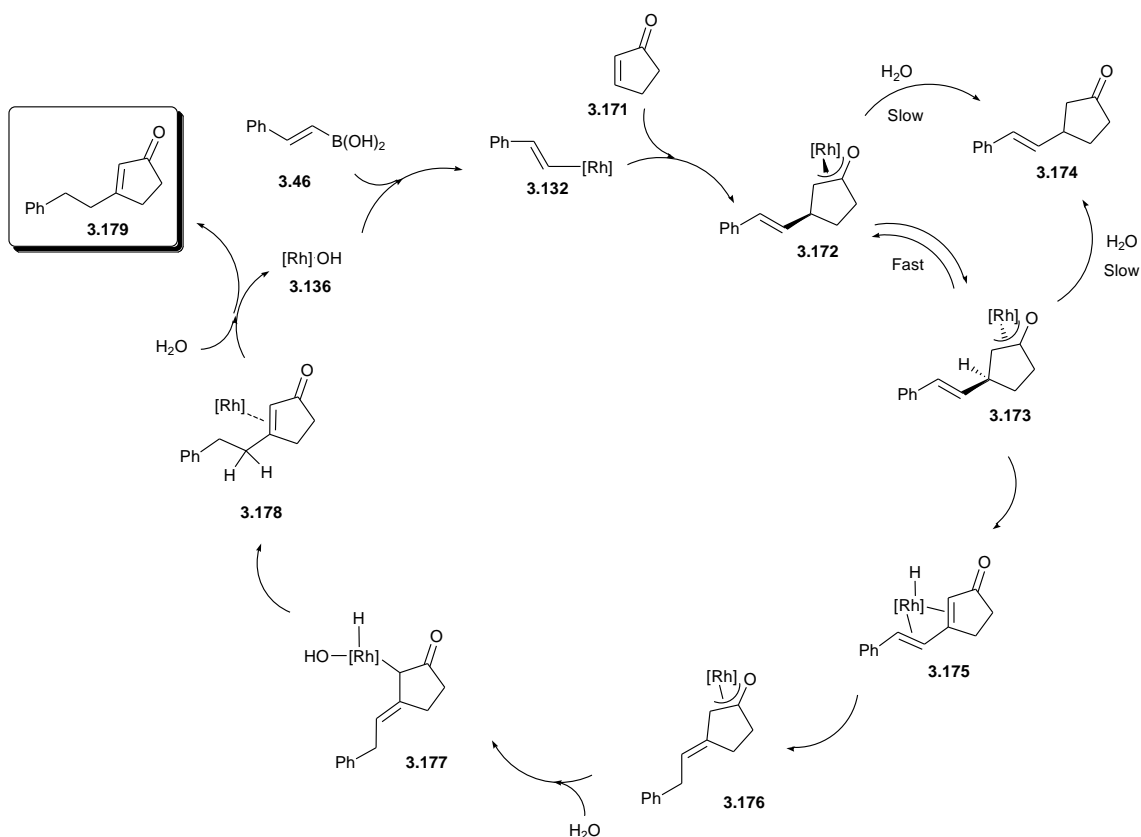
The reaction was completed in dioxane/D₂O which facilitated 130% deuterium incorporation at the α -CH₂ position. As shown in Scheme 3.43, this is from a mixture of 20% CH₂, 30% CDH and 50% CD₂ from analysis of the ¹H and ²H NMRs. This suggests α -protonation could occur from the mechanism described or as a result of some base mediated enolate formation. No deuterium was incorporated at the δ position.



Scheme 3.43

An excellent review of 1,2-, 1,4- and 1,6-additions to electron-deficient dienes by Csáky and co-workers supports the later part of the mechanism.⁹⁰ Hayashi^{91, 92} and Lautens⁹³ describe a similar mechanism for the 1,6-addition of organoboron reagents to linear $\alpha,\beta,\gamma,\delta$ -unsaturated compounds.

Interestingly the review also highlights the formation of α,β -olefins for cyclic substrates compared to β,γ -olefins for linear substrates following 1,6-additions. The catalytic cycle for α,β -olefin transposition with cyclic enones is very similar and is detailed in Scheme 3.44.

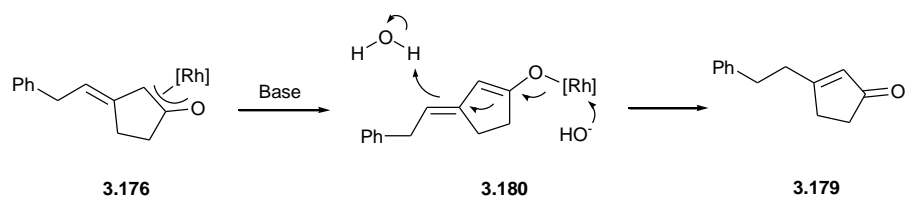


Scheme 3.44

As before, the alkenylboronic acid **3.46** is transmetalated, and the cyclic enone carbometallated to form the oxa- π -allyl species **3.172**. The alkenyl group and rhodium are delivered *syn* and must equilibrate to the *trans* diastereomer **3.173**, such that the hydrogen and rhodium are *syn* for β -hydride elimination. These diastereomers exist in equilibrium *via* the Rh-O enolate.⁶⁹ For transposition to be successful, the formation of the *trans* diastereomer and β -hydride elimination must be faster than hydrolysis. Again this is owing to the influence of the ligand and basic reaction conditions preventing protonation and promoting β -hydride elimination.

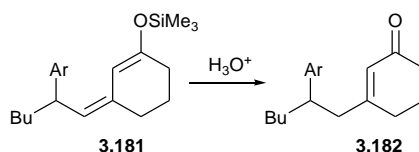
As for β,γ -olefin transposition, β -hydride elimination is followed by a 1,6-hydride addition to form oxa- π -allyl species **3.176**. Three mechanisms could then occur to complete the transposition to the α,β -olefin **3.179**.

Firstly, hydrolysis of the rhodium enolate **3.176** would afford the α,β -olefin **3.179** by selective γ -protonation (Scheme 3.45).



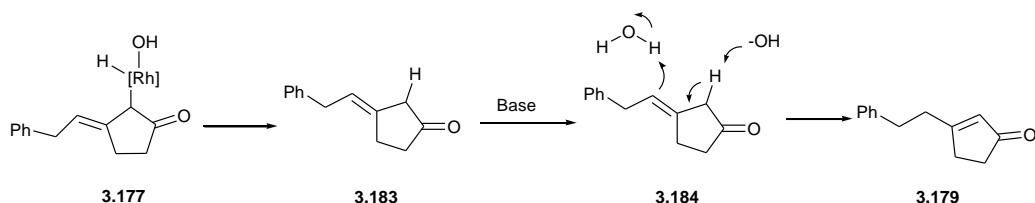
Scheme 3.45

Hayashi proposed this mechanism for an independent protonation step of a Lewis acid stabilised enolate following a 1,6-addition (Scheme 3.46).



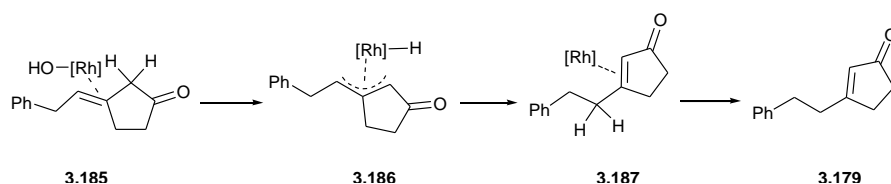
Scheme 3.46

Secondly and more preferably, hydrolysis proceeds by α -protonation of the oxa- π -allyl species **3.176**.¹⁵ This occurs *via* an oxidative addition, reductive elimination pathway *via* **3.177**.⁷⁵ α -Protonation affords the β,γ -olefin **3.183**, which as shown by Alexakis and co-workers⁹⁴ can be isomerised to the α,β -olefin **3.179** by base. This again results in γ -protonation (Scheme 3.47).



Scheme 3.47

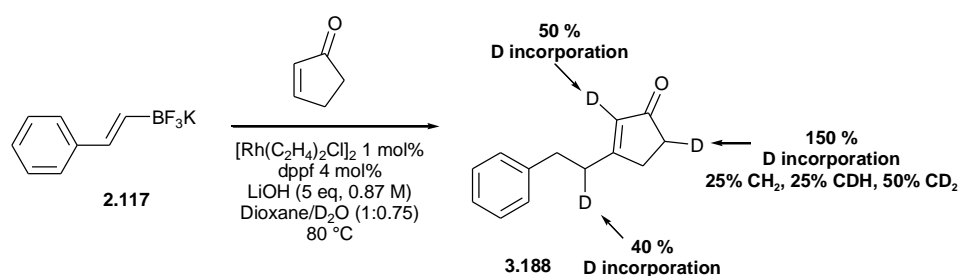
A further mechanism could occur following α -protonation (Scheme 3.48). The β,γ -olefin **3.185** can undergo standard rhodium catalysed isomerisation *via* π -allyl species **3.186**.¹⁵ Coordination of the alkene and a reversible hydrogen transfer affords the α,β -olefin **3.179**.



Scheme 3.48

Typically olefin isomerisation occurs to achieve the highest possible substitution of the double bond and afford the most thermodynamically stable product. The conformation of the cyclic compared to the linear β,γ -olefin is set up for facile rhodium co-ordination for the rearrangement. Also, the thermodynamic stability of the cyclic α,β -olefin could explain why the isomerisation to the α,β -olefin occurs with cyclic, but not linear substrates.

To determine the mechanism of hydrolysis the reaction was completed in dioxane/ D_2O to afford the deuterium labelled α,β -olefin **3.188** (Scheme 3.49).



Scheme 3.49

The first two mechanisms result in γ -protonation from water. From analysis of the 1H and 2H NMR only 40% is deuterated as CDH, a higher percentage deuterium incorporation would be expected at the γ -position resulting for these mechanisms. Considering 50% α -deuteration has occurred, α -protonation of the oxa- π -allyl species could be occurring during the reaction, or by basic enolate formation.

The α -protonation-rhodium-isomerisation is the most likely mechanism. α -Deuteration would form CDH and either the deuterium or proton could be transferred to the γ -position which accounts for 50% deuterium incorporation at the α -position (50% CD: 50% CH) and 40% deuterium incorporation at the γ position (40% CDH, 60% CH_2). Interestingly there is also 150% deuterium incorporation at the α - CH_2 position, which owing to basic enolate formation forms 25% CH_3 , 25% CDH and 50% CD_2 .

The ligand is the crucial additive that determines selectivity, it must be able to direct towards β -hydride elimination and enable isomerisation. Smaller bite angles enhance rhodium to alkene back donation, while larger bite angles promote alkene to rhodium donation. Increasing bite angles can increase the energy of activation for alkene to rhodium coordination. As bite angles increase, steric congestion around rhodium is likely to increase which sterically hinders coordination of the alkene.²¹ Interestingly, in

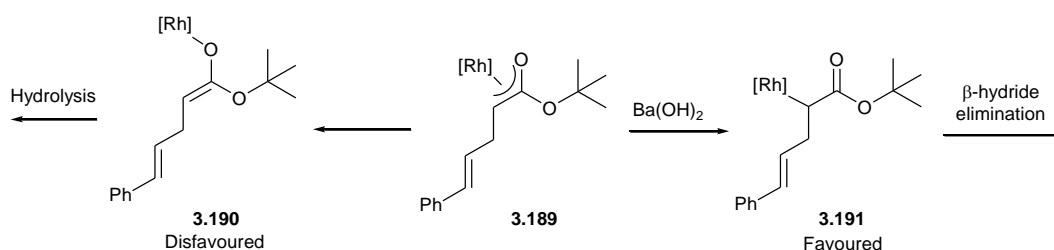
a *cis*-bidentate square planar complex, an increase in the bite angle would promote a migratory reaction.⁹⁵

A well defined bite angle can distort and hence destabilise certain geometries. As a result, it can direct the reaction by influencing the initial state, transition state or final state of the metal complex. This affects both the activity and the selectivity and even allows alternative pathways to occur.⁹⁶ Considering the findings by Zou and Lautens that smaller bite angles and rigid backbones favour β -hydride elimination, it is somewhat surprising that dppf affords olefin transposition. However, the reaction is with alkenyl rather than alkyl substrates and β -hydride elimination is only one step in the mechanism.

The ferrocenyl backbone of dppf is able to accommodate a range of bite angles owing to its flexibility which is ideal for this complex mechanism, shrinking the bite angle for alkene co-ordination and β -hydride elimination but widening the bite angle for the migratory steps.

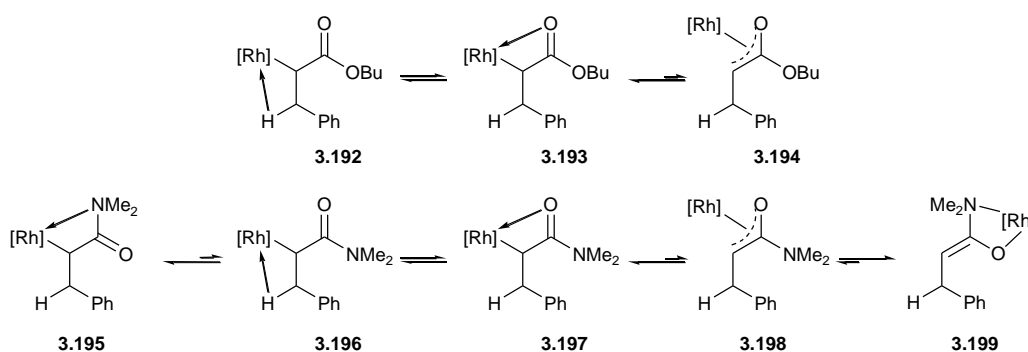
Since the carbonyl structure affects β -hydride elimination, the results obtained using *t*-butyl acrylate and acyclic β -substituted acceptors can also be rationalised.

t-Butylacrylate and N-phenethyl-acrylamide showed innate selectivity towards transposition unlike ketones. This should come as no surprise since N-phenethyl-acrylamide⁸³ and *t*-butylacrylate⁸⁵ overwhelmingly and consistently favoured β -hydride elimination over hydrolysis as they are more reluctant to enolise (Scheme 3.50).



Scheme 3.50

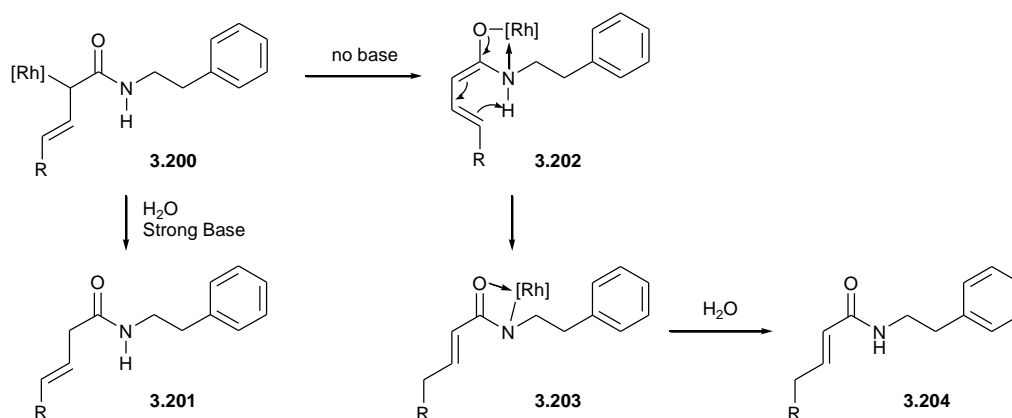
The more easily the carbonyl can coordinate to rhodium the greater the enolisation of the α -rhodium species. Ketones are readily enolisable and are normally hydrolysed unless influenced by the ligand. Although amides and esters are equally enolisable, nitrogen has a greater coordinating ability than oxygen to rhodium (Scheme 3.51). This usually means amides are more enolisable than esters, but they can be easily tuned between enolisation and β -hydride elimination.



Scheme 3.51

As β -hydride elimination is favoured when reacting alkenyl trifluoroborate salts with *t*-butylacrylate and *N*-phenethyl-acrylamide, even when using cyclooctadiene as the ligand, the transposition pathway is enabled and generation of the β,γ -olefin occurs.

Under less basic conditions using $\text{Ba}(\text{OH})_2$, *N*-phenethyl-acrylamide enabled some (18%) isomerisation to the α,β -olefin. In previous work, reaction of *N*-Phenethyl-acrylamide afforded the α,β -olefin exclusively using dppf in the absence of base. It was the only acceptor to do so. The coordinating ability of the amide under less basic conditions is providing an interesting effect and could be facilitating isomerisation to the α,β -olefin **3.204** as outlined in Scheme 3.52. The stabilised enolate **3.202** prevents α -protonation to the β,γ -olefin **3.201** and instead promotes a 1,5-hydride shift to form the α,β -olefin **3.204** via **3.203**.



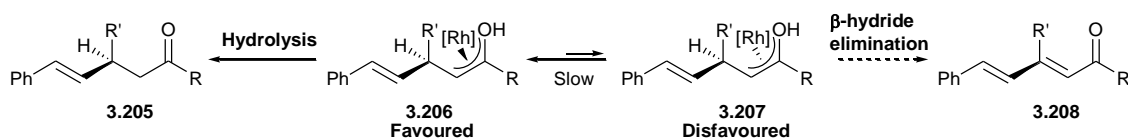
Scheme 3.52

With the addition of strong base the β,γ -olefin **3.201** is selectively obtained. This suggests base deprotonates the amine which prevents this isomerisation.

Linear β -substituted α,β -unsaturated carbonyls favoured conjugate addition. Lautens and co-workers also observed that α or β substituents on the acrylate tend to deactivate

β -hydride elimination and afford conjugate addition.⁸⁵ This may be owing to inductive σ -bond electron-donation increasing the basicity of the oxa- π -allyl species which speeds up protonation.

It could also be owing to steric hindrance promoting hydrolysis over β -hydride elimination. Formation of rhodium-oxa- π -allyl diastereomer **3.207** is slow and sterically restricted unless $R'=H$. (Scheme 3.53).



Scheme 3.53

This could also explain why a lower selectivity towards transposition was achieved for dimethylitaconate and why cyclic acceptors required harsher conditions, but can undergo olefin transposition.

3.6.11 Conclusions

The key mechanistic step that controls olefin transposition is β -hydride elimination of the oxa- π -allyl species. As the ligand had the most significant effect on transposition selectivity, it must therefore selectively direct β -hydride elimination over hydrolysis. The generated rhodium hydride completes a 1,6-addition followed by α -protonation to afford β,γ -olefins. Cyclic enones favour a further rhodium catalysed isomerisation to the more thermodynamically stable α,β -olefin. Deuterium labelling studies and literature sources support the proposed mechanism.

3.7 Chapter Conclusions

Potassium alkenyl trifluoroborate salts have been reacted in rhodium catalysed additions to α,β -unsaturated carbonyl compounds and a new transformation developed. Olefin transposition was optimised and the scope demonstrated. In general, linear α,β -unsaturated carbonyl compounds afford β,γ -olefins and cyclic α,β -unsaturated carbonyl compounds afford α,β -olefins.

Kinetic studies highlighted the protodeboronation of potassium alkenyl trifluoroborates as a major competing reaction within rhodium catalysed additions. It also demonstrated the ability of the ligand to be the directing additive between hydrolysis to afford conjugate addition and β -hydride elimination towards olefin transposition.

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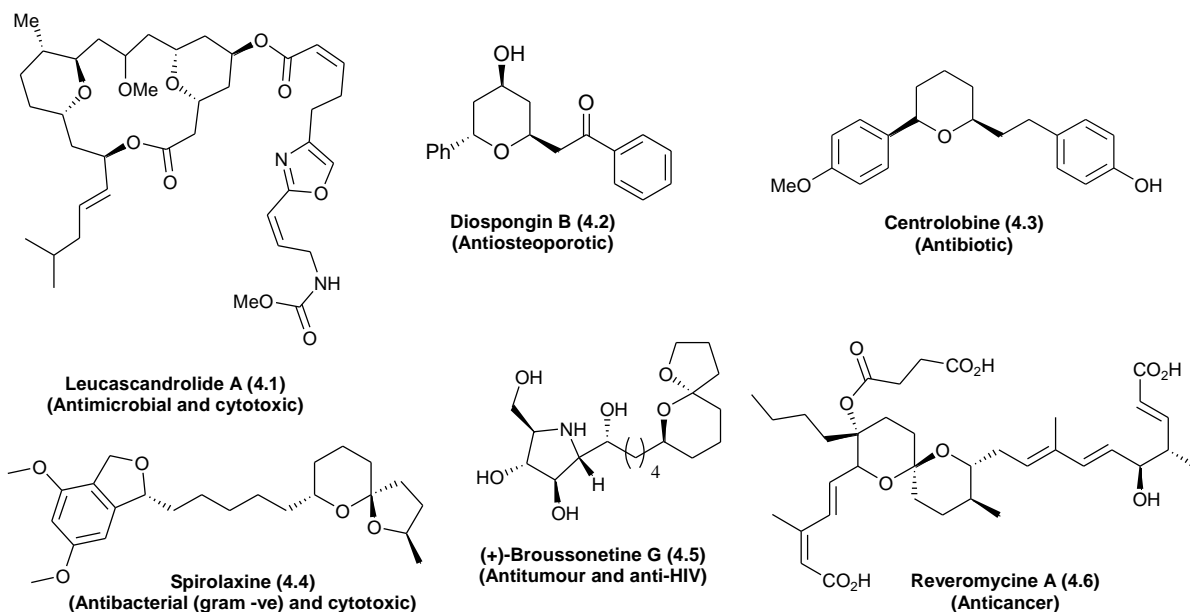
Chapter 4: Application of potassium alkenyl trifluoroborate salts in rhodium catalysed additions towards natural product synthesis

4.1. Overview and Aims

To use rhodium catalysed conjugate addition and transposition methodology towards the synthesis of natural products, their key intermediates and analogues.

4.2. Introduction

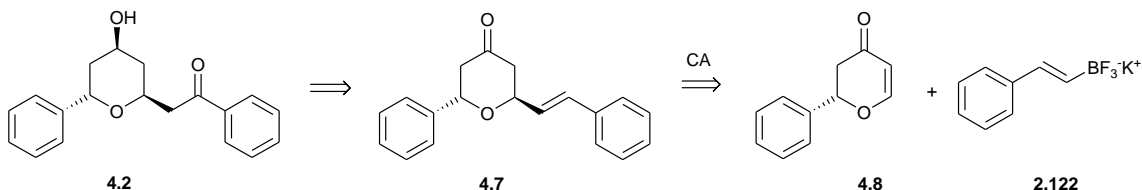
Tetrahydropyran (THP) rings are a prevalent feature in natural products. Such compounds frequently have high biological activities covering a vast array of bioactivity from anticancer, anti HIV to antibacterial. Figure 4.1 demonstrates just a handful of examples of active THP containing natural products. While the core is common, the structures can vary widely in synthetic complexity. Multiple THP rings can also be present in the form of spiroketals such as in spiroloxine **4.4** and reveromycine **4.6**.



Scheme 4.1

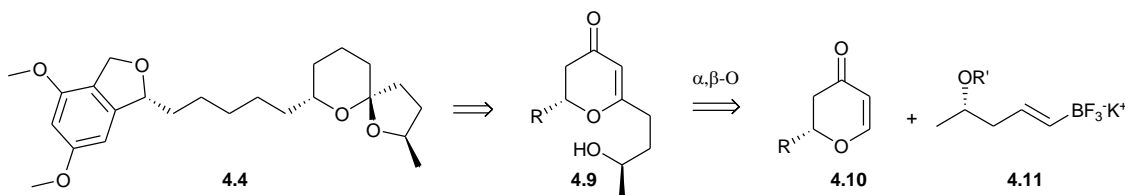
It is interesting to note that in this class of compound alkyl chains appear more frequently than aryl groups. Since we can now reliably use potassium alkenyl trifluoroborates in rhodium catalysed additions this presents a vast synthetic opportunity.

Compounds such as diospongin B **4.2** could be assembled *via* the intermediate **4.7** functionalising the alkene and carbonyl as required. The tetrahydropyranone **4.7** can be envisioned using the rhodium catalysed conjugate addition of potassium alkenyl trifluoroborate **2.122** to the relevant dihydropyranone **4.8** as shown by the general retrosynthesis in Scheme 4.1.



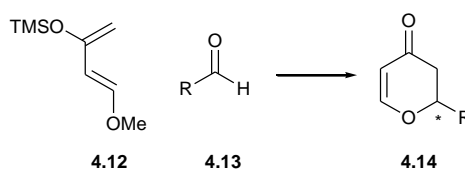
Scheme 4.1

Similarly, retrosynthesis of the spirocyclic compounds such as Spirolaxine **4.4** by ring opening leads to the common intermediate dihydropyranone **4.9** (Scheme 4.2). This could obviously be assembled using rhodium catalysed olefin transposition methodology with the desired dihydropyranone **4.10** and potassium alkenyl trifluoroborate salt **4.11** (as detailed in Chapter 3).



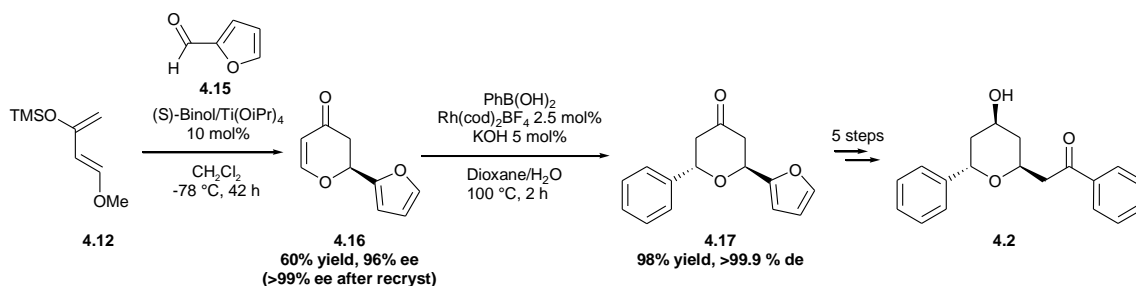
Scheme 4.2

A powerful methodology for the asymmetric synthesis of 6-membered heterocycles is Hetero-Diels-Alder (HDA) cycloaddition.^{1,2,3} This has been a key reaction for the synthesis of many THP containing natural products.⁴ Fortunately, the required 5,6-dihydro-2H-pyranones **4.14**, can be accessed using carbonyl containing heterodienophiles such as aldehydes and dienes such as Danishefskys Diene **4.12** (Scheme 4.3).^{5,6,7}



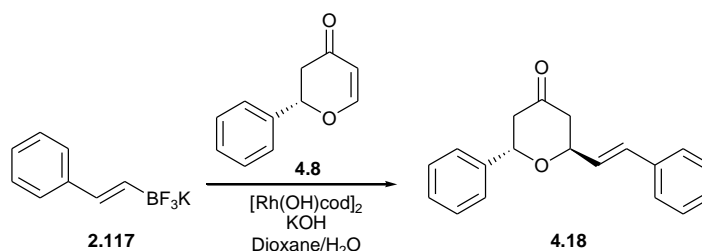
Scheme 4.3

Diospongin B **4.2** has been synthesised using the rhodium catalysed conjugate addition of phenylboronic acid to dihydropyranone **4.16** as a key step.⁸ Selective *trans* addition is accomplished by using the enantiopure acceptor which is synthesised *via* an asymmetric Hetero-Diels-Alder reaction (Scheme 4.4).



Scheme 4.4

During a previous synthesis towards diospongin, alkene **4.18** was a key intermediate. From examination of this compound, it could be more concisely assembled by rhodium catalysed conjugate addition of potassium styryltrifluoroborate **2.117** to dihydropyranone **4.8** (Scheme 4.5).



Scheme 4.5

This is a useful example as it highlights the potential for easy access to analogues of a number of natural products, by employing potassium alkenyl trifluoroborate salts. It also demonstrates the power of combining HDA and rhodium catalysed addition methodology towards the synthesis of important natural products and their derivatives.

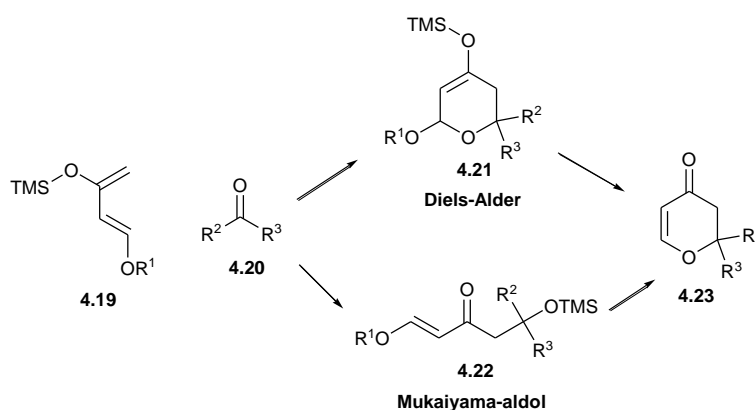
4.3 Oxa-Hetero-Diels-Alder

HDA methodology is highly stereoselective; remarkably only one out of four possible diastereomers is formed upon reaction of an aldehyde with a diene. There are two main asymmetric approaches: a dienophile with a chiral auxiliary or more economically, a chiral catalyst.

For catalytic asymmetric HDA reactions a chiral Lewis acid is essential to coordinate to the carbonyl functionality. Coordination activates the substrate and enantioselectivity is produced as the chiral environment directs the diene to approach from the least sterically hindered face. A large number of chiral Lewis acid complexes have been successfully employed.

Danishefsky first attempted the asymmetric HDA reaction^{9,10} which has since evolved as chiral catalysts have been developed. Novel, chiral Lewis-acid catalysts based on chromium, copper, titanium, aluminium and rhodium have widened the scope to unactivated aldehydes and ketones. Alongside this, activation has also been achieved *via* hydrogen bonding of chiral alcohols or amines¹¹ and through the use of organocatalysts.¹²

As detailed in Scheme 4.6, two mechanistic pathways are possible, depending on the Lewis acid employed.^{13,14} A traditional Diels-Alder cycloaddition can proceed in a step wise or concerted fashion whereas the Mukaiyama-aldol mechanism proceeds *via* an isolatable intermediate **4.22** followed by cyclisation.¹⁵



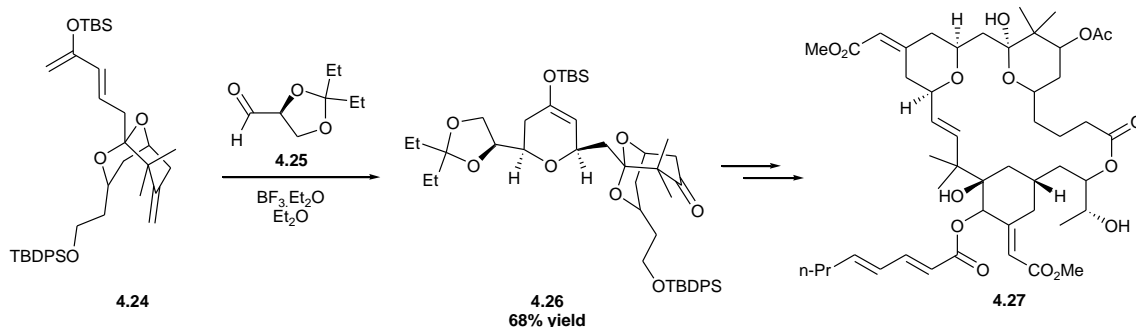
Scheme 4.6

Functionality can be varied by substituents on the diene, along with the aldehyde or ketone. For 5,6-dihydro-2H-pyranones such as **4.14**, Danishefsky's diene **4.12** would be an appropriate choice for reaction with aldehydes.

A number of potent natural products containing THP rings have employed asymmetric HDA as a key synthetic transformation. A recent review by Pellissier illustrates the vast array of natural products accessible utilising HDA methodology alongside the large variety of asymmetric conditions available.⁴

The most employed dienophiles in HDA reactions are unactivated aldehydes. Chiral dienophiles and dienes have been developed to extend the scope of the reaction. When chiral auxiliaries are used, Lewis acids are also required. BF₃·Et₂O is most commonly employed but, ZnCl₂, Yb(OTf)₃, Eu(fod)₃, La(fod)₃, Yb(fod)₃ are also used.

For example, chiral aldehyde **4.25** was employed in the asymmetric HDA reaction towards the northern hemisphere (C1-C16) of potent anticancer agent bryostatin 1 **4.27** (Scheme 4.7). The major isomer **4.26** was easily separated from minor amounts of two other diastereomers.¹⁶



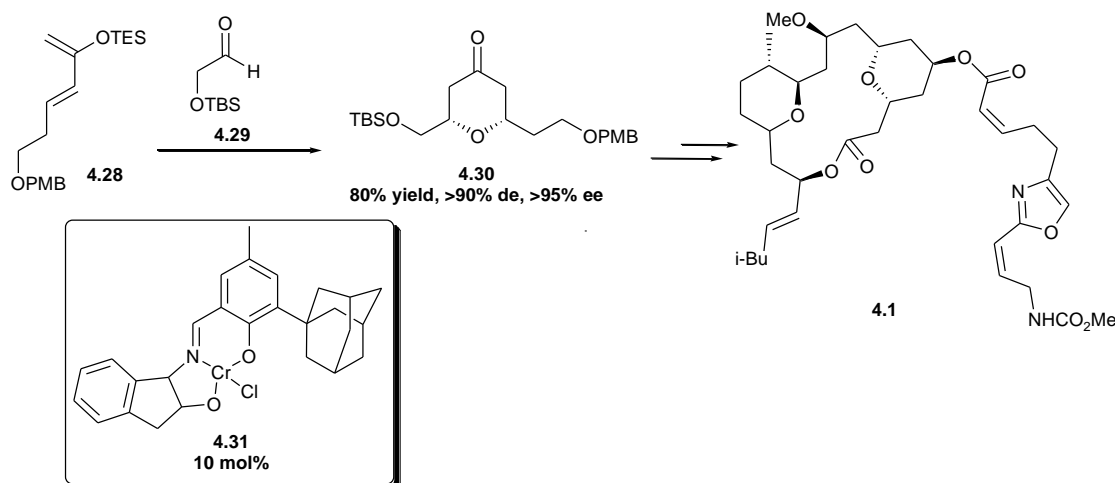
Scheme 4.7

Over the past decade, important advances have been made in the area of novel chiral catalysts which have significantly improved the methodology by facilitating milder conditions requiring 1-10 mol% catalytic loadings. These new chiral Lewis acid catalysts and organocatalysts have facilitated enantioselective cycloadditions for activated and unactivated aldehydes and ketones.

Well known catalysts include chromium, titanium and rhodium complexes, but less frequently used catalysts include copper, zinc, cobalt, manganese, aluminium, indium, magnesium, ytterbium and organocatalyst taddol.⁴

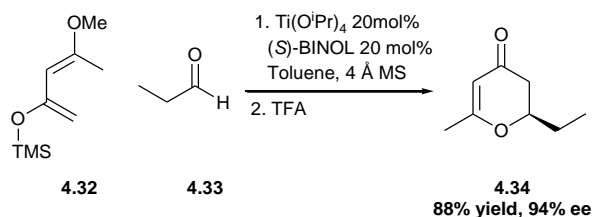
Chiral chromium-salen complexes are the most frequently applied in HDA reactions. Since their first report in 1998 by Jacobsen *et al.*¹⁷ they have been widely developed and employed in HDA reactions to synthesise a large number of compounds. Cr(II) and Cr(III) salen, porphyrin and even polymer bound complexes have been employed successfully with a range of dienes, from Danishefskys diene to highly functionalised and chiral dienes.

For example, Jacobsen's asymmetric HDA reaction between 2-siloxydiene **4.28** and aldehyde **4.29** is a key step in the sequence towards the cytotoxic macrolide (+)-leucascandrolide A (**4.1**).^{18,19} The reaction occurs in high yield with high enantio- and diastereoselectivity using catalyst **4.31** (Scheme 4.8).



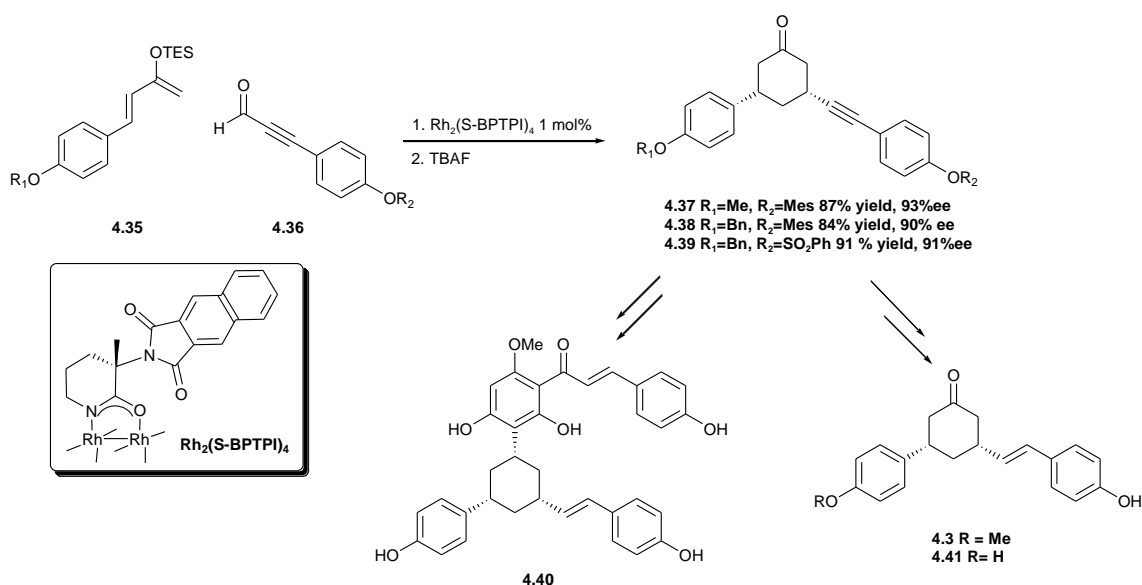
Scheme 4.8

Also highly utilised are titanium catalysts most frequently with chiral binol derived ligands.^{20,21} H₈-Binol in particular offers excellent enantioselectivities and high yields for a wide range of dihydropyranones.^{22,23} A key application was the synthesis of hepialone **4.34** in a single step using a binol-titanium catalyst (Scheme 4.9).²⁴



Scheme 4.9

Chiral rhodium complexes are also utilised to catalyse HDA reactions. Chiral dirhodium(II)carboxylate and carboxamidate complexes demonstrate tremendous power in highly enantioselective reactions at very low (even 0.01 mol%) catalytic loadings.²⁵ Several similar natural products of interest have been synthesised using these conditions. Antibiotic centrolobine **4.3**, antileishmanial agent de-O-methylcentrolobine **4.41**²⁶ and antitumour agent calyxin L **4.40**,²⁷ can be accessed *via* intermediates **4.37**, **4.38** and **4.39** synthesised by a Rh₂(S-BPTPI)₄ catalysed asymmetric HDA (Scheme 4.10).



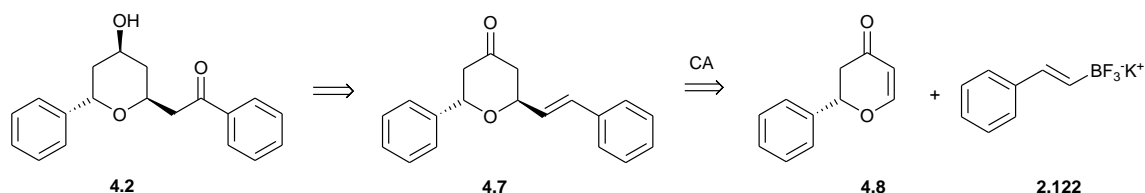
Scheme 4.10

Other successful catalytic systems for the enantioselective HDA reaction of aldehydes and Danishefsky's diene include $\text{Cu}(\text{OTf})_2$ with chiral bisoxazoline ligands,²⁸ ZnEt_2 and 3,3'- Br_2BINOL ,²⁹ $\text{Co}(\text{III})$ triflate complex with 1,2-bis(3,5-dimethylphenyl)-1,2-ethylenediamine³⁰ and (salen) $\text{Mn}(\text{III})$ complexes.³¹ Owing to the instability of many Lewis acid catalysts in air and water, many catalysts require *in situ* preparation immediately prior to the reaction. In light of this several air stable and storable Lewis acid catalysts have been synthesised using zirconium,^{32,33} ytterbium,^{34,35} cerium,³⁶ indium³⁷ and magnesium.³⁸ Additionally, organocatalysts, predominantly TADDOL derivatives have been developed³⁹ and proceed with excellent enantioselectivities in high yields.¹¹

The array of different conditions has been developed to improve enantioselectivity and yields for different functionality on the dienes and dienophiles. Many of the accessed natural products exhibit biological activity, but assembly of different analogues would require different dienes and dienophiles which could require different conditions for high yields and enantioselectivity. By combining HDA and conjugate addition methodologies, similar derivatives would be quickly and easily accessible from core intermediates to synthesise analogues in a high throughput fashion.

4.4 Key dihydropyranones and their synthesis *via* the Oxa-Hetero-Diels-Alder reaction

A number of natural products, their precursors and analogues would be accessible by combining HDA and rhodium catalysed addition methodologies. Of particular interest is diospongins B **4.2**, which can be considered retrosynthetically from dihydropyranone **4.8** as shown in Scheme 4.2



Scheme 4.2

Centrolobine **4.3**, de-O-methylcentrolobine **4.41** and diarylheptanoid **4.42**⁴⁰ have a very similar general structure that is also common to a number of other natural products including calyxin L **4.40**, rhoiptelol **4.43** and blepharocalyxin D **4.44**. Interestingly these are all *cis* substituted THPs, but *trans* diastereomers often also have biological activities, sometimes with greater potency, therefore synthesis of *trans* diastereomers such as **4.45** would be interesting (Figure 4.2). With these compounds in mind, dihydropyranones such as **4.46** and **4.47** would be useful.

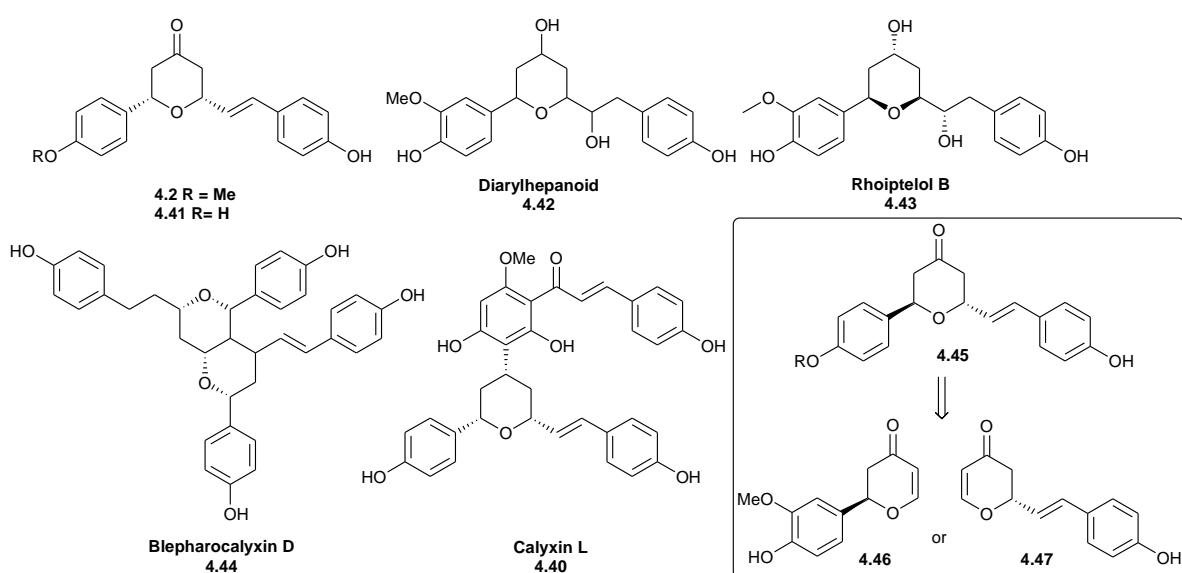
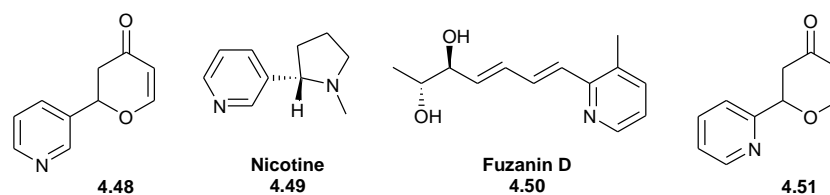


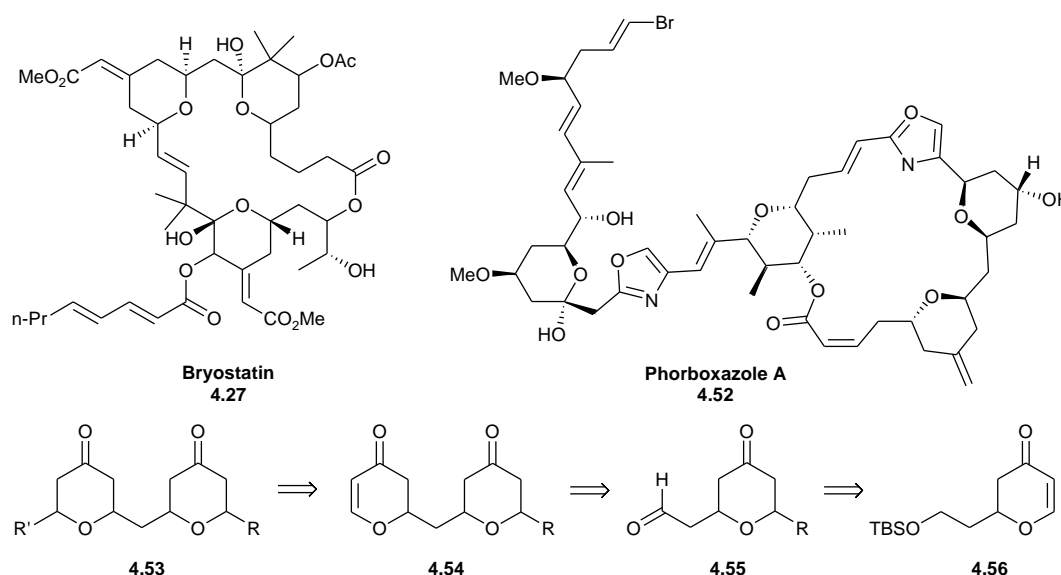
Figure 4.2

Pyridines are biologically relevant moieties. 3-pyridines are found in nicotine **4.49**⁴¹ while 2-pyridines are present in natural products such as cytotoxic fuzanin D **4.50**⁴² (Scheme 4.11). Additions to dihydropyrones **4.48** and **4.51** could therefore present biologically interesting molecules.



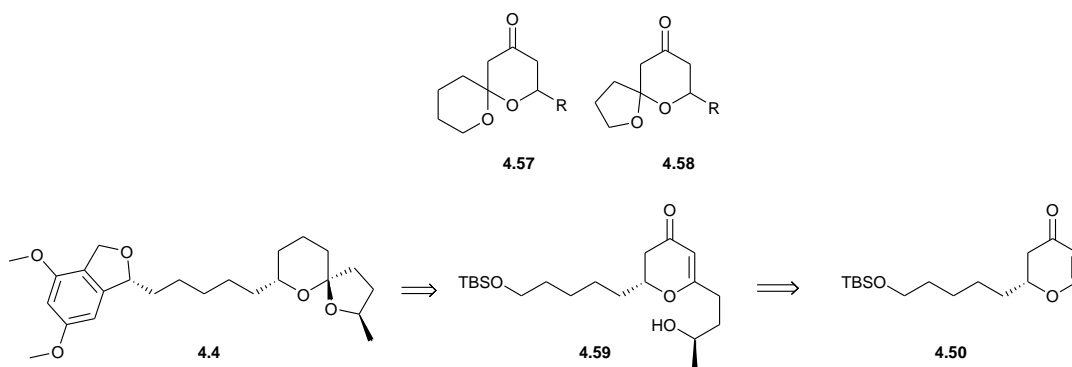
Scheme 4.11

Compound **4.53** is a key fragment pattern in a number of natural products including bryostatin **4.27** and phorboxazole A **4.52**. It could be accessed *via* a HDA-conjugate addition-HDA sequence as illustrated in Scheme 4.12. This would require the dihydropyrene **4.56**.



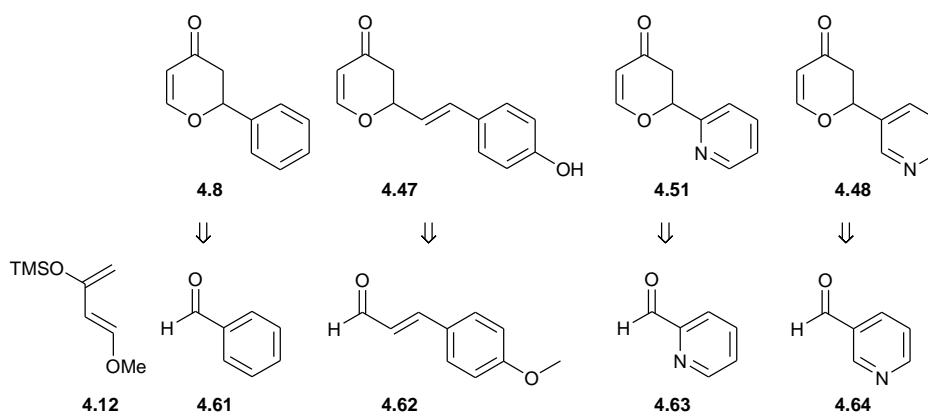
Scheme 4.12

6,6 and 5,6 spirocyclic cores (**4.57**, **4.58**) are both prevalent features and worthy of synthesis. Spirolaxine **4.4** in particular represents an interesting challenge where the dihydropyranone **4.50** would be a useful precursor (Scheme 4.13).



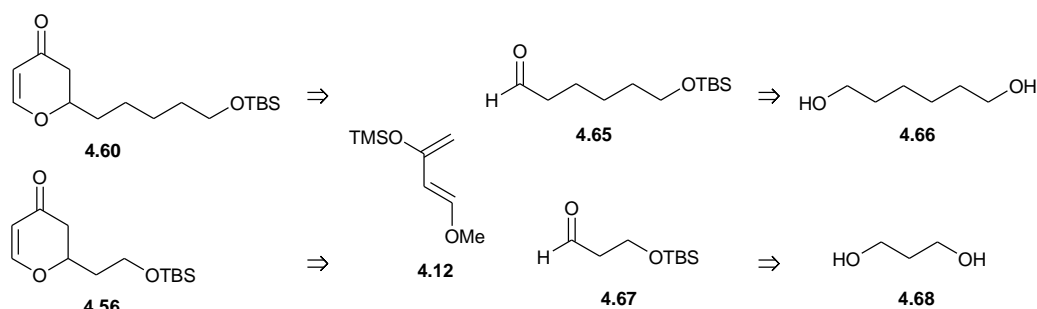
Scheme 4.13

With these compounds in mind, synthesis of the relevant dihydropyranones using HDA methodology would require Danishefsky's diene **4.12** and unactivated commercially available aldehydes **4.61-4.64** as shown in Scheme 4.14.



Scheme 4.14

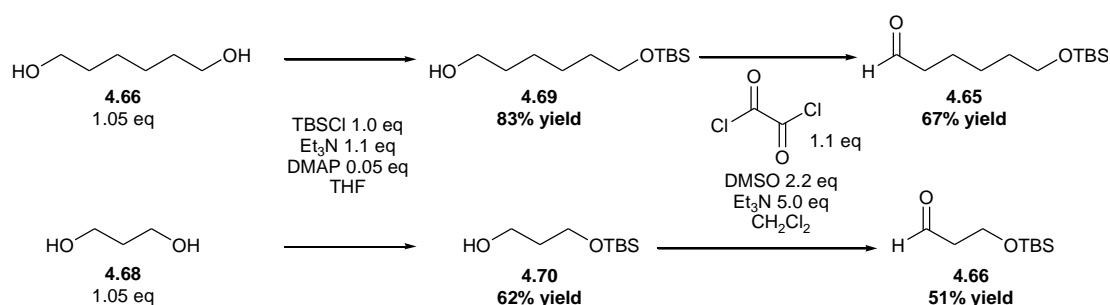
Dihydropyranones **4.60** and **4.56** require alkyl aldehydes **4.65** and **4.67** which could be synthesised from commercially available diols **4.66** and **4.68** as shown in Scheme 4.15.



Scheme 4.15

Hexane-1,6-diol **4.66** and 1,3-propanediol **4.68** were monoprotected with TBSCl under standard conditions to afford **4.69** and **4.70** in 83% and 62% yield respectively (Scheme 4.16). This was followed by Swern oxidation to afford aldehydes **4.65** and **4.67** in 67%

and 51% yields respectively. Once purified, these aldehydes were stored in the freezer to prevent decomposition.



Scheme 4.16

Danishefsky's diene **4.12** is a popular diene for the HDA reaction. It has a facile synthesis, which can be readily completed on a multigram scale in quantitative yield (Scheme 4.17). ZnCl₂ is reacted with anhydrous Et₃N for 1 h at room temperature before the addition of (*E*)-4-methoxybut-3-en-2-one **4.71** in benzene. On a 10 g scale, dropwise addition of TMSCl is necessary and a suitable exit needle is required to appropriately vent the HCl gas produced whilst maintaining an inert atmosphere. The reaction is stirred at 40 °C for 24 h and quenched at room temperature by the addition of dry Et₂O. The resulting mixture is filtered through neutral alumina until all residual solids are removed; on a large scale multiple filtrations are sometimes necessary. Evaporation of the solvent *in vacuo* afforded Danishefsky's diene **4.12** as a red oil in quantitative yield. Once isolated, it was stored at 4 °C under nitrogen.



Scheme 4.17

With Danishefsky's diene and desired aldehydes in hand, the next step was to apply them under Lewis acid catalysed HDA conditions to initially synthesise racemic dihydropyranones. BF₃·Et₂O is a widely used Lewis acid for HDA reactions, but often requires temperatures between 0 °C and -78 °C. HDA reactions with ZnCl₂ on the other hand can be conducted at room temperature and with the reagent readily available, it was initially chosen for the racemic HDA of the chosen aldehydes with Danishefsky's diene. The corresponding dihydropyranones were synthesized on 1 g scale (Table 4.1).

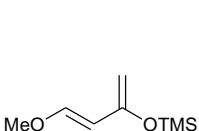

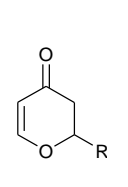
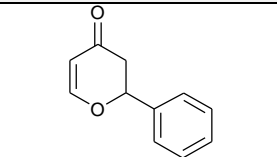
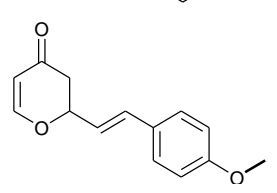
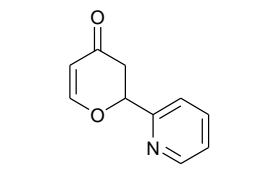
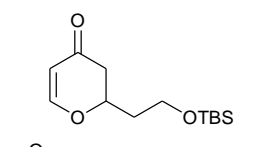
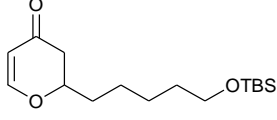
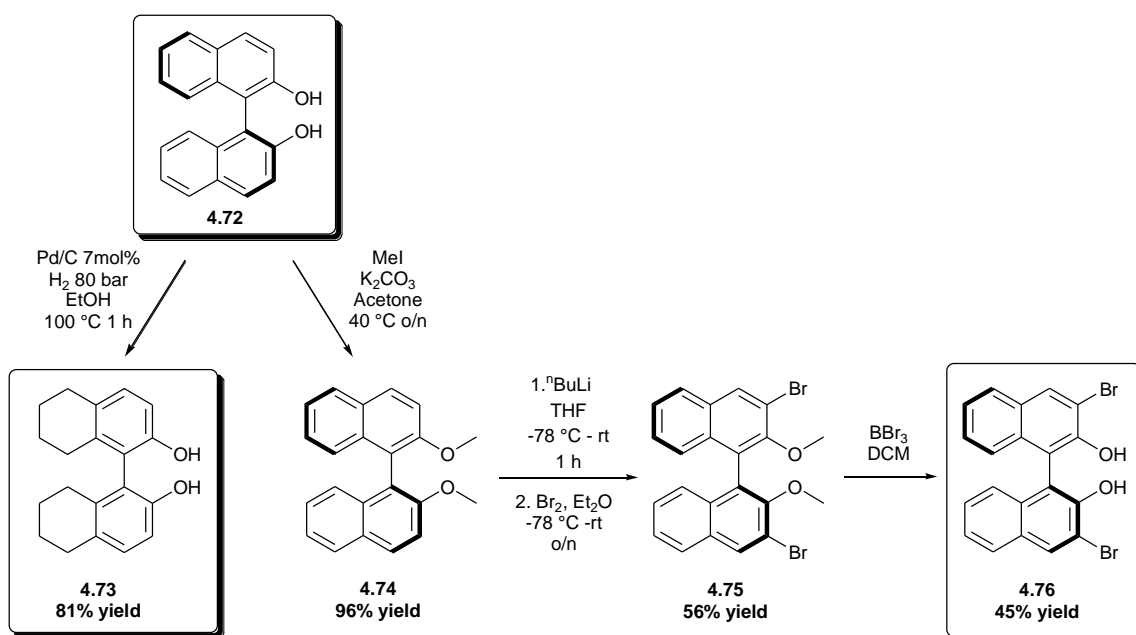
 <p>4.12</p>	<p>1. </p> <p>ZnCl₂ 3 mol% Et₂O 3 mol% Benzene, rt 2. CF₃COOH</p>	
Dihydropyrone	Compound No.	Yield
	4.8	98%
	4.47	20%
	4.51	90%
	4.56	40%
	4.60	81%

Table 4.1

Yields were variable across the different functionality. The low yield of **4.47** highlights the benefit of using addition methodology over HDA to implement alkenyl side chains.

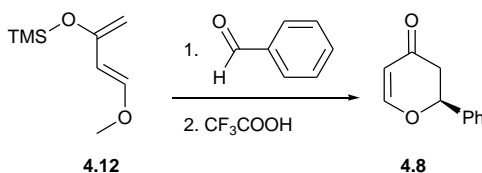
From the context of our work, chiral catalysts would be the most appropriate solution to synthesise the corresponding dihydropyranones enantioselectively. As previously discussed there are a number of chiral catalysts reported for the reaction, but in the interest of time and costs, catalysts and ligands available in the lab were prioritised.

Popular conditions for Danishefsky's diene and aldehydes include ZnEt₂ and 3,3'-Br₂-binoI²⁹ and Ti(ⁱOPr)₄ and binol derived ligands. Feng and co-workers demonstrated that H₈-binol > H₄-binol > binol for the HDA of aldehydes and Danishefsky's diene catalysed by Ti(OⁱPr₄).⁴³ Therefore binol derivatives 3,3'-Br₂-binol (**4.76**) and H₈-binol (**4.18**) were synthesised as outlined in Scheme **4.18**.



Scheme 4.18

Benzaldehyde was reacted with Danishefsky's diene following literature conditions for ZnEt_2 , $\text{Ti}(\text{O}^i\text{Pr})_4$ and binol derived ligands. Small fluctuations in temperatures greatly affected enantioselectivity. Maintaining the reaction between $-5 - 5^\circ\text{C}$ afforded the highest enantioselectivities. The results outlined in Table 4.2 highlight $\text{Ti}(\text{O}^i\text{Pr})_4$ and H_8 -binol afford the highest yield and enantioselectivity.



Catalyst	Ligand	Solvent	% Yield	%ee
Et_2Zn	Br_2 -Binol	Toluene ^a	62%	75%
		DCM ^a	10%	20%
$\text{Ti}(\text{O}^i\text{Pr})_4$	Binol	Toluene ^b	91%	80%
	Br_2 -Binol	Toluene ^b	61%	20%
	H_8 -binol	Toluene ^b	85%	90%

a)- 25°C , b) 0°C

Table 4.2

Aldehydes were freshly purified by distillation where possible before reaction with Danishefsky's diene under $\text{Ti}(\text{O}^i\text{Pr})_4$ and H_8 -binol catalysis. Chiral dihydropyranones

4.77-4.81 were isolated with mixed success in moderate yield and enantioselectivities (Table 4.3). Once isolated, the dihydropyranones were stored under nitrogen at -20 °C

Dihydropyrone	Compound No.	% Yield	% ee
	4.77	85%	90%
	4.78	16%	44%
	4.79	61%	14%
	4.80	24%	62%
	4.81	57%	67%

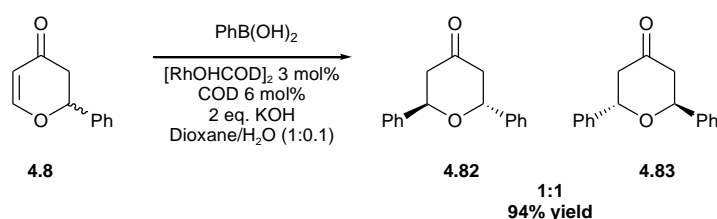
Table 4.3

Again cinnamaldehyde reacted very poorly and with low enantioselectivity to afford **4.78** in 16% yield and 44% ee. Alkyl dihydropyranones **4.80** and **4.81** were isolated in moderate yields with modest enantioselectivities.

4.5 Conjugate additions to dihydropyranones

To demonstrate rapid diversification and the synthesis of natural product precursors and their unnatural analogues, aryl and alkenyl organoboron reagents were employed in rhodium catalysed conjugate additions to the synthesised dihydropyranones.

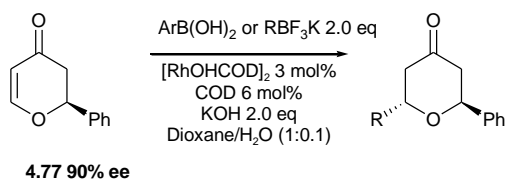
Initial stereochemical investigations were completed using *rac*-2-phenyl-2,3-dihydropyran-4-one **4.8** and phenylboronic acid. Rhodium catalysed conjugate addition as shown in Scheme 4.19 generated the symmetrical substrate in excellent yield. From HPLC analysis only 2 of the 4 possible stereoisomers were present, indicating substrate control is selective for *trans* addition.



Scheme 4.19

This result was promising and it was hoped although being less bulky, similar stereocontrol would be maintained in the addition of alkenylboronates. Therefore rhodium catalysed conjugate additions of arylboronic acids and potassium alkenyl trifluoroborates to 2-phenyl-2,3-dihydro-pyran-4-one **4.77** were completed (Table 4.4). Standard conditions employed 3 mol% $[\text{Rh(OH)(cod)}]_2$, 6 mol% cod, 2.0 eq KOH, 2.0 eq organoboron reagent in dioxane/water (10:1) at 80 °C with racemic and enantiopure dihydropyranone. The dr was determined by HPLC analysis.

Very satisfyingly all additions were completed with selective *trans* addition. THPs **4.83** and **4.89** were completed on a slightly larger scale and recrystallised to amplify the dr to >99%.



THP	Compound No.	Yield	% d.r
	4.83	96%	90% (>99% ^a)
	4.84	100%	90%
	4.85	100%	90%
	4.86	81%	92%
	4.87	72%	90%
	4.88	77%	90%
	4.89	63%	90% (>99% ^a)

a) after recrystallisation

Table 4.4

Analogues of centrolobine precursor **4.90** were completed using racemic dihydropyranone **4.47** owing to poor enantioselectivity in the asymmetric HDA and time constraints. Tetrahydropyranones **4.91-4.93** were isolated in good yield with complete *trans* selectivity, even on the less bulky dialkenyl derivative **4.93** (Table 4.5).

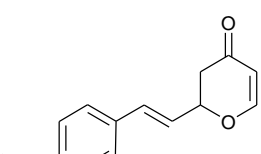
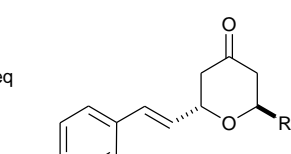
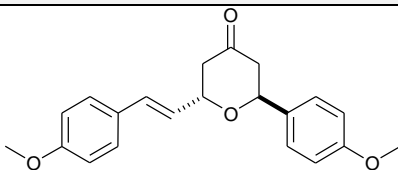
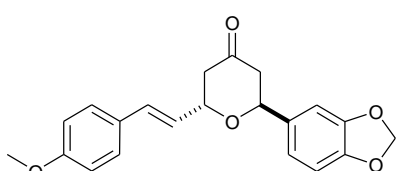
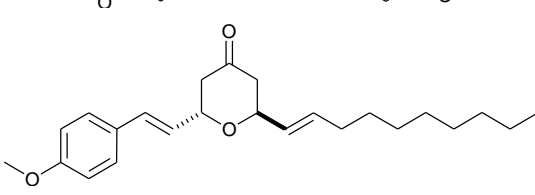
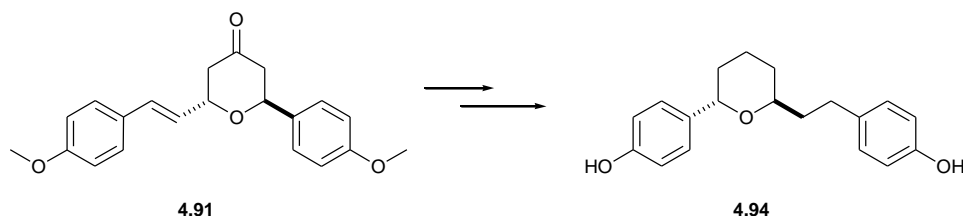
 4.47	$\xrightarrow[\text{Dioxane/H}_2\text{O (1:0.1)}]{\text{ArB(OH)}_2 \text{ or RBF}_3\text{K 2.0 eq, [RhOHCOD]}_2 \text{ 3 mol\%, COD 6 mol\%, KOH 2.0 eq}}$	 4.90
THP	Compound No.	Yield
	4.91	58%
	4.92	75%
	4.93	81%

Table 4.5

As shown by Scheme 4.20, **4.91** is a precursor to the *trans* diastereomer **4.94** of demethoxycentrolobine **4.41**, which could be accessed in two further steps using standard literature conditions.



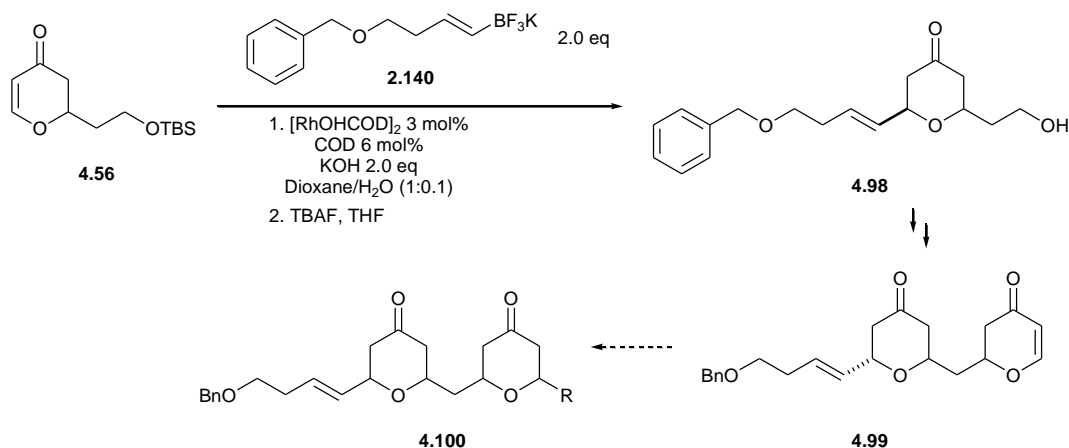
Scheme 4.20

Dihydropyranone **4.60** was reacted under standard conjugate addition conditions in moderate yield, but excellent *trans* selectivity (Table 4.6). Addition of phenylboronic acid afforded **4.96** in modest yield. Styryl trifluoroborate afforded **4.97** in poor yield, but with complete recovery of the starting dihydropyranone.

THP	Compound No.	Yield
	4.96	64%
	4.97	37% ^a
a) 63% recovery of dihydropyranone 4.65		

Table 4.6

As a precursor to phorboxazole A and bryostatin, potassium trifluoroborate **2.140** was reacted with dihydropyranone **4.56** (Scheme 4.21). Upon purification, the conjugate addition product could not be separated from unreacted dihydropyranone and therefore the mixture was exposed directly to TBAF in THF at room temperature. The deprotected alcohol **4.98** was afforded in 81% yield and indicated excellent selectivity was achieved in the conjugate addition. In the future, oxidation of the alcohol to the aldehyde could enable a second HDA to form a second dihydropyranone and ultimately common fragment **4.100**.

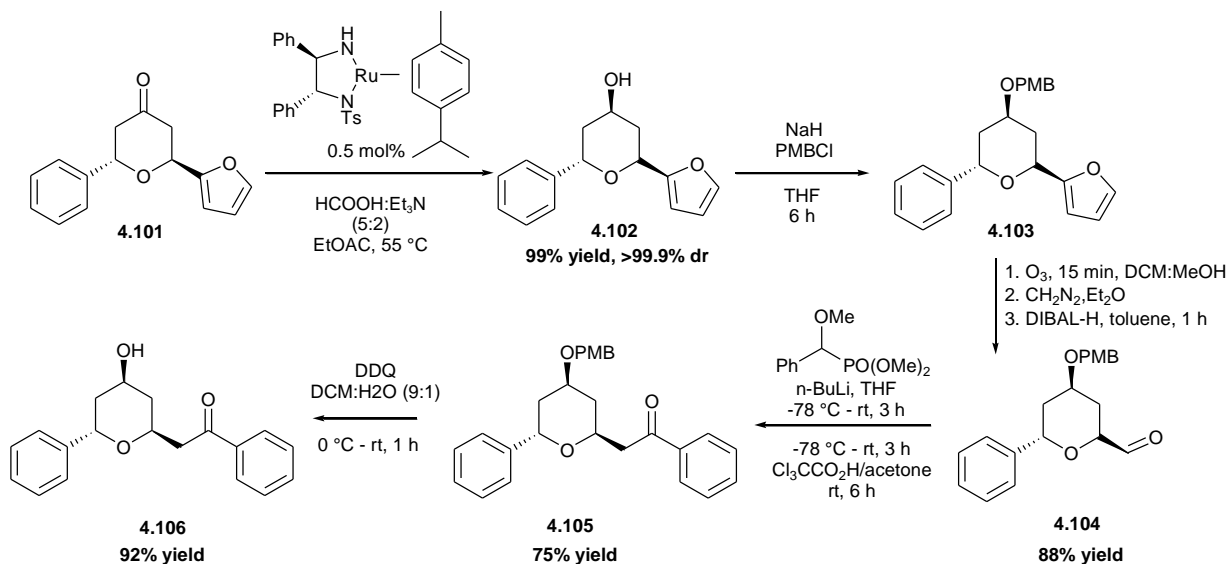


Scheme 4.21

The synthesised tetrahydropyranone rings could undergo numerous further functionalisations to natural products, their analogues and other interesting small molecules.

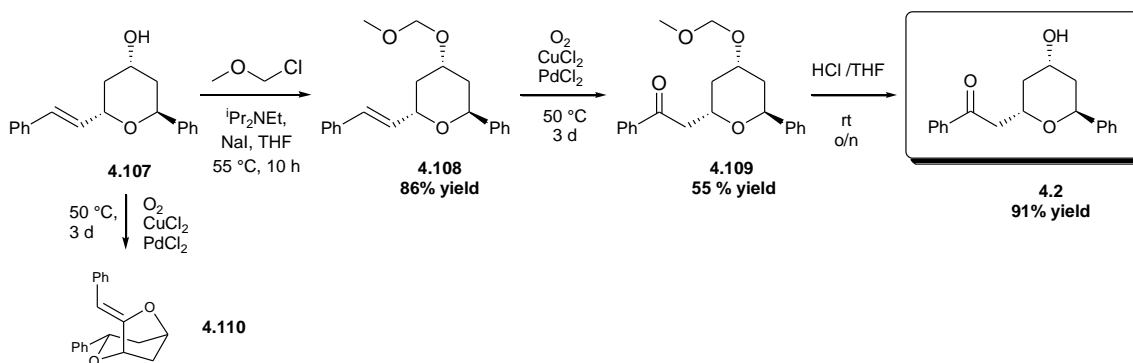
4.6 Synthesis towards Diospongins B

A number of total syntheses towards the diospongins have been reported.^{44,45,46,47} As discussed previously, diospongins B has been synthesised using conjugate addition to selectively form the *trans* product **4.101**. However, further manipulation is required to install the other side chain (Scheme 4.22). It is worth noting here that they achieve a very selective asymmetric transfer hydrogenation.



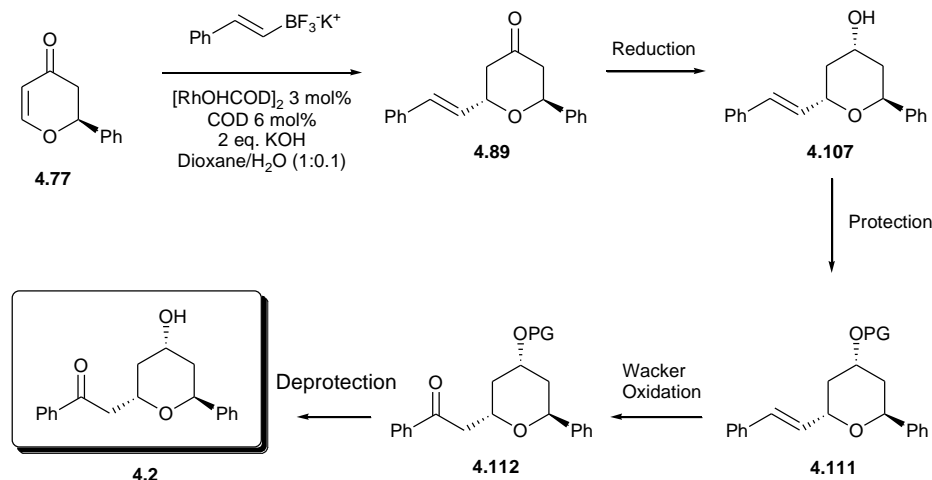
Scheme 4.22

Kawai and co-workers have previously employed intermediate **4.107** in their synthesis of diospongins B.⁴⁸ Its synthesis required 7 steps, but it is easily manipulated into diospongins B by alcohol protection and Wacker oxidation to regioselectively install the ketone (Scheme 4.23). They demonstrated that for diospongins B, where the alcohol and alkene are on the same face, protection of the alcohol is required to prevent an intramolecular Wacker oxidation from occurring which forms the bicyclic compound **4.110**.



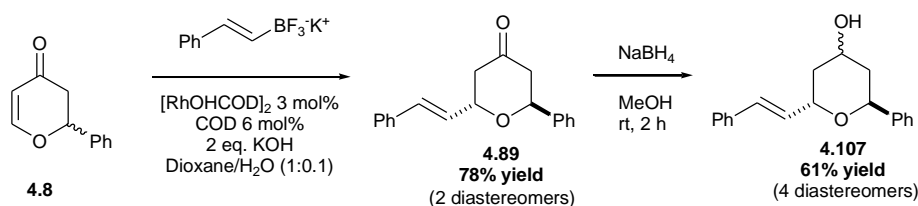
Scheme 4.23

By combining successful elements of these past synthetic routes with conjugate addition methodology of alkenyl trifluoroborates, a much more concise synthesis can be envisioned as outlined in Scheme 4.24. This reduces the total synthesis to 6 steps from commercially available starting materials and with the opportunity to easily construct analogues.



Scheme 4.24

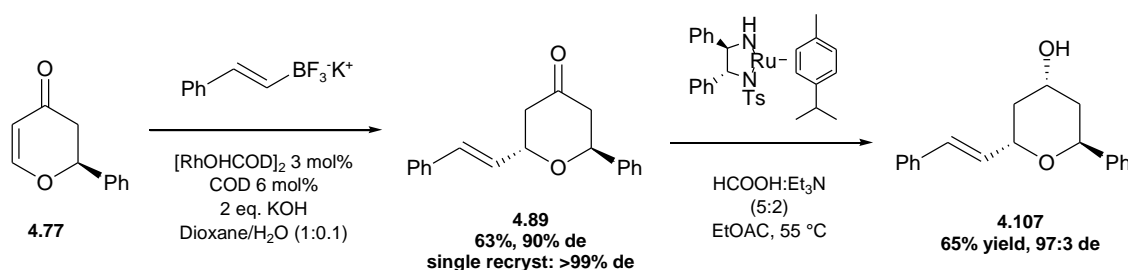
To test the methodology, racemic dihydropyranone **4.8** was initially employed. As previously discussed conjugate addition of styryltrifluoroborate was entirely *trans* selective. Achiral reduction using NaBH_4 therefore led to a mixture of 4 diastereomers of the alcohol.



Scheme 4.25

The asymmetric synthesis was attempted following the same methodology (Scheme 4.26). Rhodium catalysed conjugate addition of potassium styryltrifluoroborate to 2-phenyl-2,3-dihydro-pyran-4-one **4.77** was complete on a 1.44 mmol scale (5 times the normal scale) to afford the *trans* selective product in 63% yield with 28% recovery of the starting dihydropyranone. A single recrystallisation of the conjugate addition product **4.89** increased the de to >99%.

Following the work by Kumaraswamy and co-workers, a transfer hydrogenation using Noyori's catalyst selectively afforded alcohol **4.107** in good yield with excellent diastereomeric excess. Again this was recrystallised to improve the de to >99%.



Scheme 4.26

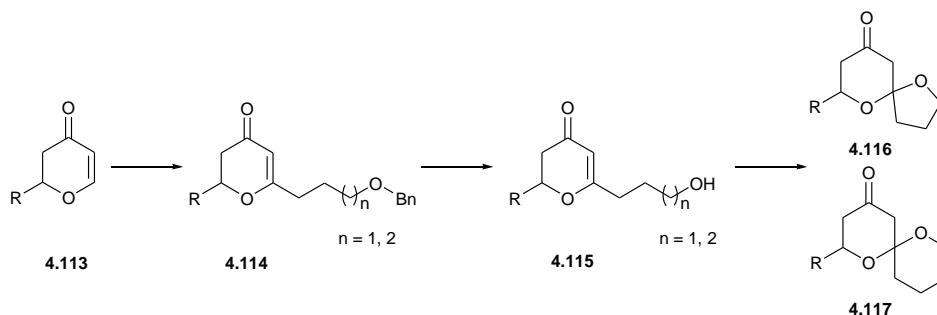
Given more time the synthesis could be completed following the standard literature conditions reported by Kawai and co-workers, as outlined earlier in Scheme 4.23.

4.7 Conclusions

Hetero-Diels-Alder methodology has been utilised to synthesise a number of racemic and enantiopure dihydropyranones in good to excellent yields and enantioselectivities. Conjugate additions of aryl boronic acids and potassium alkenyl trifluoroborate salts to dihydropyranones are *trans* selective. The THP products generated could be further functionalised to a number of natural products, precursors and their analogues. This methodology has been demonstrated towards a concise and highly stereoselective synthesis of diospongine B.

4.8 Future work

Olefin transposition to these challenging acceptors presents a future opportunity. Application of potassium alkenyl trifluoroborate salts with pendent oxygen functionality could be employed as outlined in Scheme 4.27. This would have applications in the synthesis towards natural products such as spirolaxine and aplysiatoxin.



Scheme 4.27

4.9 References

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Chapter 5: Experimental

General Considerations

Commercially available reagents and solvents were obtained from Sigma-Aldrich Company Ltd, Fisher Scientific Ltd, Lancaster Synthesis Ltd, and Strem Chemicals UK and used without further purification. 'Petrol' refers to the fraction of petroleum ether boiling in the range 40-60 °C.

All air-sensitive reactions were carried out under dry nitrogen or argon atmospheres using standard Schlenk line techniques.^[1] Dichloromethane and tetrahydrofuran were dried and degassed under an argon atmosphere over activated alumina columns using an Innovative Technology Solvent Purification System (SPS) and degassed using argon prior to use in air sensitive reactions. All secondary and tertiary amines were purified by distillation using calcium hydride as a drying agent and stored under argon in Young's ampoules over 4 Å molecular sieves.

NMR spectra were recorded on Bruker AV300 or AVANCE 400 spectrometers at 298 K unless otherwise stated. Chemical shifts (δ) are expressed in parts per million (ppm). ¹H NMR and ¹³C NMR spectra were referenced internally to residual protio-solvent. Assignments were supported by ¹³C PENDANT NMR and homo- and hetero-nuclear, one- and two-dimensional experiments as appropriate. The multiplicities of the spectroscopic data are presented in the following manner: singlet (s), broad singlet (br. s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), and multiplet (m). Coupling constants (*J*) are expressed in Hertz (Hz). The assignment of aromatic proton resonances for *para* disubstituted benzene rings has been simplified by assuming an AB system, however the characteristic features of an AA'BB' system were observed in the NMR spectra.

Analytical thin layer chromatography (TLC) was performed using commercially available aluminium backed plates coated with Merk Kieselgel 60 0.20 mm, (ALUGRAM® sil G/UV254) and visualised under ultra-violet light (254 nm), or by staining with potassium permanganate, ninhydrin or vanillin solution. Flash column chromatography was carried out using Merck Kieselgel 60 H silica gel (particle size: 0.063-0.100).

Infra red spectra were recorded on a Perkin Elmer (Spectrum 100) FT-IR spectrometer, over the range 4000-600 cm⁻¹ and averaged over 32 scans with internal calibration. Melting points were determined using a Buchi 535 melting point apparatus.

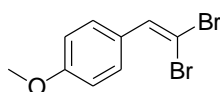
Electrospray mass spectra were obtained using a Bruker ESI-TOF or ESI-QTOF Mass Spectrometry Service at the University of Bath.

High Performance Liquid Chromatography (HPLC) was performed on a Perkin Elmer IBN series system using chiral columns such as Chiralpack OD-H by Daicel Chemical Ind. Ltd.

Gas Chromatography (GC) was performed on an Agilent 6890N Network GC System with an Agilent 19091J-413 HP-5 column (5% phenyl methyl siloxane capillary 30.0 m x 320 μ m x 0.25 μ m) and a flame ionization detector (hydrogen/air mix), injection volume: 1 μ L, carrier gas nitrogen, flow rate: 1.5 mL/min. Specific rotations were performed on an Optical Activity Ltd. AA-10 automatic polarimeter at 589nm (N D-Line) and measured at 20 °C unless otherwise stated. $[\alpha]_D^T$ values are reported in $^{\circ}\text{dm}^2\text{g}^{-1}$ as follows: $[\alpha]_D^T$, (c = g/100 mL, solvent).

5.1 Synthesis of Alkynes

5.1.1 1-(2,2-Dibromo-vinyl)-4-methoxy-benzene (2.96)

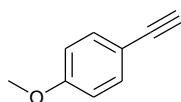


To a solution of carbon tetrabromide (4.14 g, 12.46 mmol) in CH_2Cl_2 (100 mL) was added triphenylphosphine (6.00 g, 22.8 mmol) at 0 °C and stirred for 30 mins. At 0 °C 4-methoxybenzaldehyde (1.13 g, 8.32 mmol) was then added dropwise and the reaction continued at room temperature for 2 hours. The solution was poured into excess sat. Na_2CO_3 aq. solution (25 mL) and the organic layer separated, washed with brine (25 mL), dried over magnesium sulphate, filtered and concentrated. Crude reaction mixture was taken up in petrol (100 mL) and the precipitate removed by vacuum filtration. The filtrate was concentrated *in vacuo* and then purified by flash column chromatography on silica gel (petrol/ethyl acetate 4:1) to give the dibromoalkene as a pale yellow solid (1.67 g, 69% yield).

R_f (petrol: ethyl acetate, 4:1); 0.52; Mp; 36 - 37 °C; δ_H (300 MHz; CDCl_3); 7.51 (2H, d, J 8.7 Hz, Ar); 7.41, (1H, s, ArCH); 6.89 (2H, d, J 8.7 Hz Ar); 3.83 (3H, s, OCH_3); δ_C (75.5 MHz; CDCl_3); 160.1, 136.7, 130.3, 128.2, 114.20, 87.7, 55.7

All data in accordance with literature values¹

5.1.2 1-Ethynyl-4-methoxy-benzene (2.97)

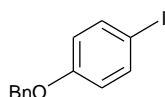


A solution of 1-(2,2-dibromo-vinyl)-4-methoxy-benzene (**2.96**) (1.67 g, 5.72 mmol) in dry tetrahydrofuran (100 mL) was cooled to -78 °C under an atmosphere of nitrogen. 2.5 M ⁿBuLi (4.6 mL, 11.4 mmol) was added dropwise at -78 °C and the reaction stirred for 1 hour. The reaction was warmed to room temperature and maintained for 1 hour. The reaction was quenched with water (25 mL) and extracted with petrol (3 x 25 mL). The organic layer was washed with brine, dried over magnesium sulphate, filtered and evaporated to afford the desired compound as an orange oil which was used in the next step without further purification (0.552 g, 92% yield).

δ_{H} (300 MHz; CDCl_3); 7.43 (2H, d, J 8.9 Hz, Ar), 6.84 (2H, d, J 8.9 Hz, Ar), 3.81 (3H, s, OCH_3), 2.30 (1H, s, CCH); δ_{C} (75.5 MHz; CDCl_3); 160.1, 133.7, 114.3, 114.0, 83.8, 75.8, 55.4; HRMS (ESI^+) *calcd* for $[\text{M}]^+$ $\text{C}_9\text{H}_8\text{O}$ m/z 132.0575 found: m/z 132.0560

All data in accordance with literature values²

5.1.3 1-Benzyloxy-4-iodo-benzene (2.99)

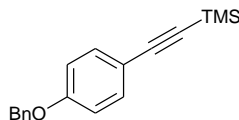


To a solution of 4-iodophenol (4.63 g, 21.05 mmol) in acetone (50 mL) was added K_2CO_3 (14.5 g, 105.24 mmol) followed by benzylbromide (2.09 mL, 17.54 mmol). The reaction was stirred under reflux for 14 h then cooled to room temperature and filtered. The mother liquor was concentrated *in vacuo* and the residue taken up in Et_2O (100 mL) and washed with water (50 mL) followed by brine (25 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford the title compound as a white crystalline solid (4.48 g, 82% yield).

R_{f} (petrol/ethyl acetate, 7:3); 0.87; Mp; 61-62 °C; ν_{max} (neat)/ cm^{-1} ; 3089, 3063, 3032 (Ar-H), 2907, 2861 (C-H), 1582, 1569 (Aryl C=C); δ_{H} (300 MHz; CDCl_3); 7.56 (2H, dt, J 9.1, 2.7 Hz, ArH), 7.44-7.31 (5H, m, ArH), 6.76 (2H, dt, J 9.1, 2.3 Hz, ArH), 5.04 (2H, s, CH_2); δ_{C} (75.5 MHz; CDCl_3); 158.6, 138.2, 136.5, 128.6, 128.1, 127.4, 117.3, 83.0, 70.0

All data in accordance with literature values³

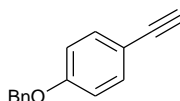
5.1.4 (4-Benzyloxy-phenylethynyl)-trimethyl-silane (2.100)



Under an inert atmosphere, trimethylsilylacetylene (3.96 mL, 28.00 mmol) was added to a mixture of 1-benzyloxy-4-iodo-benzene (**2.99**) (4.40 g, 14.00 mmol), $[\text{PdCl}_2(\text{PPh}_3)_2]$ (0.098 g, 0.14 mmol), and copper iodide (0.027 g, 0.14 mmol) in anhydrous triethylamine (35 mL). The reaction mixture was stirred at room temperature for 6 hours. Upon completion, the reaction was filtered and the filtrate concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 7:3) to isolate the title compound as a solid (3.66 g, 93% yield). R_f (petrol/ethyl acetate, 4:1); 0.91; Mp; 56-57 °C; ν_{max} (neat)/ cm^{-1} ; 3090, 3058, 3025 (Aryl C-H), 2961, 2912 (Alkyl C-H), 2156 ($\text{C}\equiv\text{C}$), 1602, 1570, 1505 ($\text{C}=\text{C}$ aryl); δ_{H} (300 MHz; CDCl_3); 7.43-7.13 (7H, m, *ArH*), 6.90 (2H, d, J 8.7 Hz, *ArH*), 5.07 (2H, s, CH_2), 0.24 (9H, s, $\text{Si}(\text{CH}_3)_3$); δ_{C} (75.5 MHz; CDCl_3); 158.9, 136.6, 133.5, 128.6, 128.1, 127.5, 115.6, 114.7, 105.1, 92.5, 70.0, 0.0; HRMS (ESI^+) *calcd* for $\text{C}_{18}\text{H}_{21}\text{OSi}$ $[\text{M}+\text{H}]^+$ m/z 281.1362 found: m/z 281.1334.

All data in accordance with literature values ⁴

5.1.5 1-Benzyloxy-4-ethynyl-benzene (2.101)



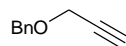
Potassium bicarbonate (6.14 g, 44 mmol) was dissolved in anhydrous methanol (50 mL) and (4-benzyloxy-phenylethynyl)-trimethyl-silane (**2.100**) (3.56 g, 12.7 mmol) was added. The reaction was stirred at 25 °C for 2 hours and then filtered and the filtrate concentrated. The residue was taken up in ethyl acetate (75 mL) and washed with water (25 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1). The title compound was isolated as orange needles (2.28 g, 86% yield).

R_f (petrol/ethyl acetate, 4:1); 0.69; Mp 66-69 °C; ν_{max} (neat)/ cm^{-1} ; 3272 ($\equiv\text{C-H}$), 2981, 2875 (alkyl C-H), 2105 ($\text{C}\equiv\text{C}$), 1600, 1568, 1505 (aryl $\text{C}=\text{C}$); δ_{H} (300 MHz; CDCl_3); 7.46-7.31 (7H, m, *ArH*), 6.92 (2H, dt, J 8.9, 2.5 Hz, *ArH*), 5.08 (2H, s, CH_2), 3.00 (1H,

s, CH); δ_C (75.5 MHz; $CDCl_3$); 159.1, 136.5, 133.6, 128.6, 128.1, 127.4, 114.8, 114.4, 83.6, 75.8, 70.0

All data in accordance with literature values⁴

5.1.6 Prop-2-ynyloxymethyl-benzene (2.103)

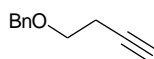


To a solution of propargyl alcohol (6 mL, 130.07 mmol) in anhydrous DMF (100 mL) at 0 °C, was slowly added sodium hydride 60% in mineral oil, (4.535 g, 113.37 mmol). After stirring for 30 minutes, benzylbromide (13.47 mL, 113.37 mmol) was added dropwise and the reaction stirred at ambient temperature overnight. The reaction was quenched at 0 °C by the dropwise addition of water (10 mL). The reaction mixture was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were washed with HCl (25 mL) followed by brine (25 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 8:2) to afford the title compound as a colourless oil (9.003 g, 60% yield).

R_f (petrol/ethyl acetate, 4:1); 0.73; ν_{max} (neat)/ cm^{-1} ; 3295 ($C\equiv C-H$); 3064, 3031 (aryl C-H); 2016 ($C\equiv C$); 1496, 1455 ($C=C$ aromatic); 1069, 1029 (C-O); δ_H (300 MHz; $CDCl_3$); 7.40-7.29 (5H, m, ArH), 4.63 (2H, s, $ArCH_2$), 4.19 (2H, d, J 2.4 Hz, OCH_2), 2.48 (1H, t, J 2.4 Hz, CCH); δ_C (75.5 MHz; $CDCl_3$); 137.2, 128.4, 128.1, 127.9, 79.6, 74.6, 71.5, 57.0; HRMS (ESI^+) *calcd* for $[M+Na]^+$ $C_{10}H_{10}ONa$ m/z 169.0629 found: m/z 169.0688

All data in accordance with literature values⁵

5.1.7 But-3-ynyloxymethyl-benzene (2.104)



A solution of but-3-yn-1-ol (2.7 mL, 35.67 mmol) in anhydrous THF (20 mL) was added dropwise over 10 min at 0 °C to a stirred solution of NaH (60% in mineral oil) (1.7 g, 42.8 mmol) and Bu_4NI (0.184 g, 0.499 mmol) in anhydrous THF (30 mL) under an inert atmosphere. The reaction was maintained at 10-15 °C by an external cold water bath. Once $H_{2(g)}$ evolution ceased, benzylbromide (3.39 mL, 28.5 mmol) was added dropwise to the reaction mixture and after 15 minutes the reaction was warmed to room temperature overnight. A few drops of water were added cautiously at 0 °C to quench

excess NaH. The reaction mixture was diluted with hexane (75 mL) and washed with brine. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 8:2) to afford the title compound as a colourless oil (4.66 g, 100% yield).

R_f (petrol/ethyl acetate, 4:1); 0.77; ν_{\max} (neat)/cm⁻¹; 3296 (CC-H), 3078, 3046 (aryl C-H), 2869 (alkyl C-H), 2109 (C≡C), 1603, 1584, (aryl C=C); δ_{H} (300 MHz; CDCl₃); 7.36-7.27 (5H, m, ArH), 4.57 (2H, s, ArCH₂), 3.61 (2H, t, *J* 7.0 Hz, OCH₂CH₂), 2.51 (2H, td, *J* 7.0, 2.7 Hz, OCH₂CH₂), 2.00 (1H, t, *J* 2.7 Hz, CH); δ_{C} (75.5 MHz; CDCl₃); 138.0, 128.4, 127.7, 81.3, 73.0, 69.3, 68.4, 19.9

All data in accordance with literature values⁶

5.1.8 (1-Methyl-prop-2-ynyloxymethyl)-benzene (2.105)

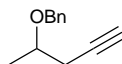


A solution of but-3-yn-2-ol (5.59 mL, 71.34 mmol) in anhydrous THF (20 mL) was added dropwise over 10 min at 0 °C to a stirred solution of NaH (60% in mineral oil) (3.29 g, 85.6 mmol) and Bu₄NI (0.369 g, 0.999 mmol) in anhydrous THF (30 mL) under an inert atmosphere. The reaction was maintained at 10-15 °C. Once H_{2(g)} evolution ceased, benzylbromide (6.78 mL, 57 mmol) was added dropwise to the reaction mixture and after 15 minutes the reaction was warmed to room temperature overnight. A few drops of water were added cautiously at 0 °C to quench excess NaH. The reaction mixture was diluted with hexane (75 mL) and washed with brine. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 8:2) to afford the title compound as a colourless oil (8.273 g, 91% yield).

R_f (petrol/ethyl acetate, 4:1); 0.79; ν_{\max} (neat)/cm⁻¹; 3072 (CC-H), 2981, 2830 (aryl C-H), 2668, 2554 (alkyl C-H), 2081 (C≡C), 1601, 1583, (aryl C=C); δ_{H} (300 MHz; CDCl₃); 7.39-7.27 (5H, m, ArH), 4.81 (1H, d, *J* 11.7 Hz, OCHH), 4.52 (1H, d, *J* 11.7 Hz, OCHH), 4.22 (1H, qd, *J* 6.6, 2.0, CH₃CH), 2.47 (1H, d, *J* 2.0, CCH), 1.49 (3H, t, *J* 6.6 Hz, CH₃); δ_{C} (75.5 MHz; CDCl₃); 137.8, 128.4, 128.0, 127.7, 83.7, 73.1, 70.5, 64.2, 22.0

All data in accordance with literature values⁷

5.1.9 (1-Methyl-but-3-ynyloxymethyl)-benzene (2.106)

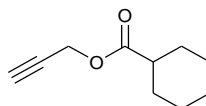


A solution of pent-4-yn-2-ol (5.58 mL, 59.44 mmol) in anhydrous THF (20 mL) was added dropwise over 10 min at 0 °C to a stirred solution of NaH (60% in mineral oil) (2.74 g, 71.3 mmol) and Bu₄NI (0.307 g, 0.83 mmol) in anhydrous THF (30 mL) under an inert atmosphere. The reaction was maintained at 10-15 °C by an external cold water bath. Once H_{2(g)} evolution ceased, benzylbromide (5.60 mL, 47.55 mmol) was added dropwise to the reaction mixture and after 15 minutes the reaction was warmed to room temperature overnight. A few drops of water were added cautiously at 0 °C to quench excess NaH. The reaction mixture was diluted with hexane (75 mL) and washed with brine. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 8:2) to afford the title compound as a colourless oil (7.832 g, 96% yield).

R_f (petrol/ethyl acetate, 4:1); 0.81; δ_H (300 MHz; CDCl₃); 7.24-7.14 (5H, m, ArH), 4.46 (2H, s, ArCH₂), 3.59 (1H, sextet, *J* 6.1, CH₃CHCH₂), 2.40 (1H, ddd, *J* 16.6, 5.0, 2.7 Hz, CHCHH), 2.25 (1H, ddd, *J* 16.6, 7.0, 2.7, CHCHH), 1.90 (1H, t, *J* 2.7, CCH), 1.20 (3H, d, *J* 6.2, CH₃); δ_C (75.5 MHz; CDCl₃); 138.5, 128.3, 127.6, 127.5, 81.2, 73.2, 70.7, 69.9, 26.0, 19.5

All data in accordance with literature values⁸

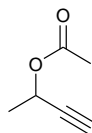
5.1.10 Cyclohexanecarboxylic acid prop-2-ynyl ester (2.108)



Propargyl alcohol (1.00 g, 17.84 mmol) was dissolved in pyridine (20 mL) and cooled to 0 °C. Cyclohexanecarbonyl chloride (4.74 mL, 35.68 mmol) was added and the reaction stirred overnight at room temperature. The solvent was evaporated and crude product purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 4:1) to afford the title compound as a colourless oil (2.3 g, 78% yield).

R_f (petrol/ethyl acetate, 4:1); 0.60; ν_{\max} (neat)/ cm^{-1} ; 2961 (CC-H), 2907, 2875 (alkyl C-H), 2156 ($\text{C}\equiv\text{C}$), 1659 ($\text{C}=\text{O}$); δ_{H} (300 MHz; CDCl_3); 4.66 (2H, d, J 2.3 Hz, CCH_2O), 2.45 (1H, t, J 2.5 Hz, CCH), 2.35 (1H, tt, J 11.3, 3.6 Hz, COCH), 1.95-1.89 (2H, m, CyH), 1.78-1.62 (3H, m, CyH), 1.52-1.4 (2H, m, CyH), 1.35-1.18 (3H, m, CyH); δ_{C} (75.5 MHz; CDCl_3); 175.2, 77.9, 74.6, 51.7, 42.9, 28.8, 25.7, 25.3

5.1.11 Acetic acid 1-methyl-prop-2-ynyl ester (2.110)

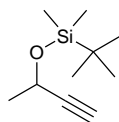


But-3-yn-2-ol (1.12 mL, 14.27 mmol) was dissolved in dichloromethane (20 mL). Triethylamine (3.0 mL, 21.4 mmol) and acetic anhydride (1.48 mL, 1.70 mmol) were added followed by DMAP (0.174 g, 1.43 mmol). The reaction was stirred overnight at ambient temperature and then poured into a saturated solution of NH_4Cl (20 mL). The mixture was separated and the aqueous layer washed with dichloromethane (20 mL). Combined organic washings were washed with 2M HCl (20 mL) followed by brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 4:1) to afford the title compound as a yellow oil (1.41 g, 81% yield).

R_f (petrol/ethyl acetate, 4:1); 0.66; ν_{\max} (neat)/ cm^{-1} ; 3294, (CC-H), 2993, 2976, 2944, (C-H), 2122 ($\text{C}\equiv\text{C}$), 1737 ($\text{C}=\text{O}$); δ_{H} (300 MHz; CDCl_3); 5.40 (1H, qd, J 6.7, 2.2 Hz, CH_3CH), 2.43 (1H, d, J 2.1 Hz, CCH), 2.05 (3H, s, COCH_3), 1.48 (3H, d, J 6.7 Hz, CH_3CH); δ_{C} (75.5 MHz; CDCl_3); 169.7, 82.1, 72.8, 59.9, 21.1, 20.9

All data in accordance with literature values⁹

5.1.12 *tert*-Butyl-dimethyl-(1-methyl-prop-2-ynyloxy)-silane (2.111)



To a solution of but-3-yn-2-ol (1.12 mL, 14.27 mmol), imidazole (1.069 g, 15.70 mmol) and DMAP (0.087 g, 0.71 mmol) in dichloromethane (20 mL), *tert*-butyldimethylsilyl chloride (2.8 g, 18.55 mmol) was added portionwise. The reaction was stirred at room temperature for 12 h and then diluted with brine (20 mL). The layers were separated and

the organic layer dried over MgSO_4 , filtered and concentrated under reduced pressure. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (1.23 g, 47% yield).

R_f (petrol/ethyl acetate, 4:1); 0.83; ν_{max} (neat)/ cm^{-1} ; 2957 (C-H), 2930, 2887, 2858 (C-H) δ_{H} (300 MHz; CDCl_3); 4.51 (1H, qd, J 6.5, 2.1 Hz, CH_3CH), 2.36 (1H, d, J 2.1 Hz, CCH), 1.42 (3H, d, J 6.5 Hz, CH_3CH), 0.90 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.13 (3H, s, $\text{Si}(\text{CH}_3)_3$), 0.12 (3H, s, $\text{Si}(\text{CH}_3)_3$); δ_{C} (75.5 MHz; CDCl_3); 86.4, 71.1, 58.8, 25.8, 18.2, -4.7, -5.0

All data in accordance with literature values¹⁰

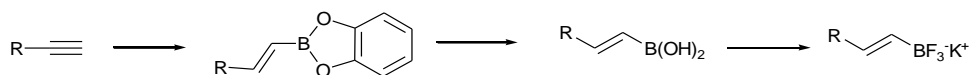
5.2 Synthesis of potassium alkenyl trifluoroborate salts

5.2.1 General procedure *via* route A for the synthesis of potassium alkenyl trifluoroborate salts



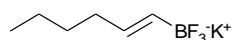
To a solution of alkyne (1.00 g, 12.17 mmol) in anhydrous dichloromethane at 0 °C was added $\text{HBBr}_2 \cdot \text{SMe}_2$ (1M solution in dichloromethane) (12.17 mL, 12.17 mmol) under nitrogen. The solution was stirred at 0 °C for 15 min then warmed to room temperature and stirred for 4 hours. Subsequently the light green solution was added to a mixture of diethyl ether/water (5:2) at 0 °C. The mixture was stirred at room temperature for 15 min. The aqueous layer was separated and the organic phase washed with cold water, followed by brine, dried over magnesium sulphate and filtered. The filtrate was concentrated *in vacuo* and fresh diethyl ether (10 mL) added. KHF_2 (0.84 g, 10.84 mmol) was added followed by addition of water (4.5 mL) over 30 min. After stirring at room temperature for 3 hours the solution was concentrated. Crude product was dissolved in acetone, filtered and the filtrate evaporated to dryness. The resulting solid was purified by dissolving in minimum hot acetone and precipitating with diethyl ether in the freezer overnight, subsequently the solution was filtered to afford the products as solids.

5.2.2 General procedure *via* route B for the synthesis of potassium alkenyl trifluoroborate salts



A mixture of catecholborane (0.45 mL, 4.2 mmol) and alkyne (0.55 g, 4.2 mL) were stirred under an inert atmosphere at 70 °C for 4 hours. The reaction was cooled to room temperature, water (2 mL) was added and the reaction stirred overnight. Diethyl ether (15 mL) was added, followed by KHF_2 and the reaction stirred for 3 hours. The reaction mixture was then concentrated *in vacuo* and the crude residue dissolved in acetone and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by recrystallisation from acetone/diethyl ether to afford the products as solids.

5.2.3 Potassium (*E*)-hex-1-enyl trifluoroborate (2.113)

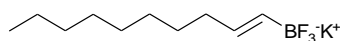


Under route A, 1-hexyne (1.00 g, 12.17 mmol) was reacted to afford the title compound as a fluffy white solid (1.31 g, 0.57% yield).

Mp; >250 °C; ν_{max} (film)/ cm^{-1} ; 2960, 2927, 2874, 2858 (C-H), 1640 (C=C); δ_{H} (300 MHz; MeOD); 5.78 (1H, dt, J 17.5, 6.0 Hz, CHCHB); 5.36 (1H, dqd, J 17.6, 3.9, 1.6 Hz, CHCHB); 2.02-1.95 (2H, m, CHCH₂); 1.40-1.30 (4H, m, CH₂CH₂CH₃); 0.89 (3H, t, J 7.1 Hz, CH₃); δ_{C} (126 MHz; MeOD); 138.2, 36.6, 33.0, 23.4, 14.4 (C-B not observed); δ_{B} (160 MHz; MeOD); 3.31; δ_{F} (471 MHz; MeOD); -142.8

All data in accordance with literature values¹¹

5.2.4 Potassium (*E*)-dec-1-enyltrifluoroborate (2.114)

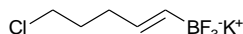


Under route A, 1-decyne (0.55 g, 4.02 mmol) was reacted to afford the title compound as a fluffy white solid (0.445 g, 45% yield).

Mp; >250 °C; ν_{max} (neat)/ cm^{-1} ; 2955, 2922, 2852 (C-H), 1642 (C=C); δ_{H} (500 MHz; MeOD); 5.79 (1H, dt, J 18.0, 5.9 Hz, CHCHB), 5.36 (1H, d, J 18.0 Hz, CHCHB), 2.00-1.96 (2H, m, CHCH₂), 1.33-1.25 (12H, m, (CH₂)₆CH₃), 0.90 (3H, t, J 7.1 Hz, CH₃); δ_{C}

(126 MHz; MeOD); 138.1, 136.7, 36.9, 33.1, 30.7, 30.6, 30.5, 23.7, 14.4; δ_B (160 MHz; MeOD); 3.43; δ_F (471 MHz; MeOD); -142.6; HRMS (ESI) *calcd* for $[M]^+ C_5H_8BClF_3$ m/z 171.0360 found: m/z 171.0371
All data in accordance with literature values¹²

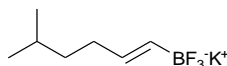
5.2.5 Potassium (*E*)-5-chloro-pent-1-enyltrifluoroborate (2.115)



Under route B, 5-chloropentyne (1.56 g, 15.25 mmol) was reacted to afford the title compound as a white solid (0.57 g, 20% yield).

Mp; >250 °C; ν_{max} (neat)/cm⁻¹; 2961, 2939 (C-H), 1637 (C=C), 625 (C-Cl); δ_H (300 MHz; D₂O); 5.95 (1H, dt, *J* 18.4, 6.3 Hz, BCHCH), 5.48 (1H, dqt, *J* 19.0, 4.1, 2.9 Hz, BCHCH), 3.63 (2H, t, *J* 6.6 Hz, ClCH₂), 2.22-2.15 (2H, m, CH₂CH), 1.85 (2H, quintet, *J* 6.6 Hz, CH₂CH₂CH₂), δ_C (75.5 MHz; D₂O); 136.6, 136.5, 45.8, 34.1, 34.1; δ_B (96 MHz; D₂O); 3.34; δ_F (376 MHz; MeOD); -137.5; HRMS (ESI) *calcd* for $[M]^+ C_5H_8BClF_3$ m/z 171.0360 found: m/z 171.0371

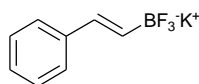
5.2.6 Potassium (*E*)-5-methyl-hex-1-enyl-borane (2.116)



Under route B, 5-methyl-hex-1-yne (2.00 g, 20.8 mmol) was reacted to afford the title compound as a grey powder (2.83 g, 72% yield).

Mp; >300 °C; ν_{max} (neat)/cm⁻¹; 3005, 2960, 2926 (C-H), 1644 (C=C), 1422, 1364 (C-H), 1223, 1093, 995 (B-F); δ_H (500 MHz; MeOD); 5.78 (1H, dt, *J* 17.7, 6.0 Hz, CHCHB), 5.35 (1H, dd, *J* 17.7, 3.8 Hz, CHCHB), 2.02-1.94 (2H, m, CH₂CHCH), 1.56 (1H, septet, *J* 6.7 Hz, CH(CH₃)₂), 1.26-1.22 (2H, m, (CH₃)₂CHCH₂), 0.88 (6H, d, *J* 6.7 Hz, CH(CH₃)₂); δ_C (75.5 MHz; CDCl₃); 138.5, 138.4, 40.1, 34.8, 28.7, 23.1, 22.9
 δ_B (96 MHz; MeOD); 3.99; δ_F (470 MHz; MeOD); -142.7; HRMS (ESI) *calcd* for $[M]^+ C_7H_{13}BF_3$ m/z 165.1062 found: m/z 165.1070

5.2.7 Potassium *trans*-styryltrifluoroborate (2.117)

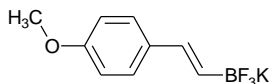


Phenylacetylene (5.00 g, 49 mmol) was reacted under route A to afford the title compound as a white solid (4.63 g, 45% yield).

Mp; >250 °C; ν_{max} (neat)/cm⁻¹; 3006, 2981, 2965 (C-H), 1623 (C=C), 1247, 1091, 974 (B-F); δ_{H} (400 MHz; MeOD); 7.36 (2H, d, *J* 7.2 Hz, *ArH*), 7.23 (2H, t, *J* 7.7 Hz, *ArH*), 7.10 (1H, tt, *J* 7.3, 1.3 Hz, *ArH*), 6.72 (1H, d, *J* 18.4 Hz, *CHCHB*), 6.26 (1H, dq, *J* 18.3, 3.9 Hz, *CHCHB*); δ_{C} (75.5 MHz; MeOD); 142.2, 137.1, 129.6, 127.7, 127.3 (no C-B observed); δ_{B} (96 MHz; MeOD); 4.05; δ_{F} (376 MHz; MeOD); -142.8

All data in accordance with literature values ¹³

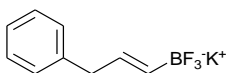
5.2.8 Potassium (*E*)-2-(4-methoxy-phenyl)-vinyl-trifluoroborate (2.118)



Under route B, 1-ethynyl-4-methoxy-benzene (**2.97**) (0.55 g, 4.2 mmol) was reacted to afford the title compound as a white solid (0.21 g, 21% yield).

Mp; >250 °C; δ_{H} (300 MHz; MeOD); 7.30 (2H, d, *J* 8.7 Hz, *Ar*), 6.81 (2H, d, *J* 8.8 Hz, *Ar*), 6.66 (1H, d, *J* 19.0 Hz, *CHCHB*), 6.10 (1H, dq, *J* 14.4 Hz, 3.3 Hz, *CHCHB*), 3.78 (3H, s, *OCH*₃); δ_{C} (75.5 MHz; MeOD); 159.2, 143.9, 127.8, 114.7, 55.8 (C-B not observed); δ_{B} (96 MHz; MeOD); 4.25; δ_{F} (376 MHz; MeOD); -141.0

5.2.9 Potassium (*E*)-3-phenyl-propenyl-trifluoroborate (2.119)

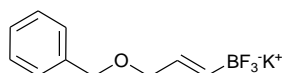


Prop-2-ynylbenzene (1.00 g, 8.6 mmol) was reacted under route B to afford the title compound as a white power (0.68 g, 31% yield).

Mp; >250 °C; ν_{max} (neat)/cm⁻¹; 3016, 2984 (C-H), 1637 (C=C), 1604, 1494 (aryl C=C); δ_{H} (300 MHz; D₂O); 7.19-7.33 (2H, m, *ArH*), 7.28-7.22 (3H, m, *ArH*), 7.07 (1H, dt, *J*

17.9, 6.2 Hz, *CHCHB*), 5.49-5.39 (1H, m, *CHCHB*), 3.37 (2H, d, *J* 6.2 Hz, *ArCH₂*); δ_C (126 MHz; MeOD); 143.2, 136.6, 129.6, 129.1, 126.4, 43.4 (no C-B observed); δ_B (160 MHz; MeOD); 3.17; δ_F (471 MHz; MeOD); -142.8; HRMS (ESI⁻) *calcd* for [M]⁻ C₉H₉BF₃ *m/z* 185.0794 found: *m/z* 185.0758

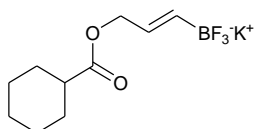
5.2.10 Potassium (*E*)-3-benzyloxy-propenyl-trifluoroborate (2.120)



Prop-2-ynyloxymethyl-benzene (**2.103**) (1.37 g, 9.4 mmol) was reacted under route B to afford the title compound as a white powder (1.37 g, 57% yield)

Mp; decomposes at 129 °C; ν_{\max} (neat)/cm⁻¹; 3060, 3032, 2981, 2879 (C-H), 1650 (C=C), 1073 (C-O); δ_H (300 MHz; MeOD); 7.10 - 7.00 (5H, m, *ArH*), 5.56 (1H, dt, *J* 12.2, 6.5 Hz, *CHCHB*), 5.22 (1H, dd, *J* 17.6, 3.8 Hz, *CHCHB*); 4.27 (2H, s, *ArCH₂O*), 2.16 - 2.07 (1H, m, *CHCH₂O*), 1.91 - 1.82 (1H, m, *CHCH₂O*); δ_C (75.5 MHz; MeOD); 140.2, 138.8, 129.3, 128.9, 128.5, 76.8, 71.4 (no C-B observed); δ_B (96 MHz; MeOD) 3.24; δ_F (471 MHz; MeOD); -142.7; HRMS (ESI⁻) *calcd* for [M]⁻ C₁₀H₁₁BF₃O₁ *m/z* 215.0855 found: *m/z* 215.0848

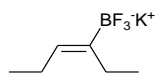
5.2.11 Potassium (*E*)-(3-((cyclohexanecarbonyl)oxy)prop-1-en-1-yl) trifluoroborate (2.121)



Cyclohexanecarboxylic acid prop-2-ynyl ester (**2.108**) (3.00 g, 18 mmol) was reacted under route B to afford the title compound as a white powder (0.69 g, 18% yield).

Mp; >250 °C; ν_{\max} (neat)/cm⁻¹; 2956, 2929 (C-H), 1721 (C=O), 1643 (C=C), 1296, 1275 (C-O); δ_H (500 MHz; MeOD); 5.79 (1H, dt, *J* 17.3, 6.7 Hz, *CHCHB*), 5.40-4.42 (1H, m, *CHCHB*), 2.01 (2H, d, *J* 7.2 Hz, *OCH₂*), 1.58 (1H, quintet, *J* 6.5 Hz, *CH₂CHCH₂*), 1.31 (2H, q, *J* 7.2 Hz, *CHCH₂*), 1.26 (2H, q, *J* 7.2 Hz, *CH₂CH*), 0.93-0.89 (6H, m, *CH₂CH₂CH₂*); δ_C (126 MHz; MeOD); 185.8, 138.4, 83.6, 40.1, 28.7, 23.0, 22.9 (no C-B observed); δ_B (96 MHz; MeOD); 3.70; δ_F (471 MHz; MeOD); -142.7; HRMS (ESI⁻) *calcd* for [M]⁻ C₁₀H₁₅BF₃O₂ *m/z* 235.1117 found: *m/z* 235.1119

5.2.12 Potassium (*E*)-1-ethyl-but-1-enyl-trifluoroborate (2.122)

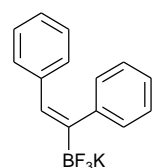


Hex-3-yne (2.00 g, 24.35 mmol) was reacted under route A to afford the title compound as a white solid (1.83 g, 40%).

Mp; >250 °C; ν_{\max} (neat)/cm⁻¹; 2962, 2931, 2871 (C-H), 1630 (C=C); δ_{H} (500 MHz; MeOD); 5.52 (1H, t, *J* 6.8 Hz, CHCH₂), 2.06-2.00 (4H, m, (CH₂CCH₂CH₃), 0.94 (6H, t, *J* 7.6 Hz, (CH₃, CH₃); δ_{C} (126 MHz; MeOD); 132.2, 23.8, 23.0, 21.6, 15.3 (C-B not observed); δ_{B} (96 MHz; MeOD); 4.75; δ_{F} (471 MHz; MeOD); -144.3; HRMS (ESI⁻) *calcd* for [M]⁻ C₆H₁₁BF₃ *m/z* 151.0906 found: *m/z* 151.0918.

All data in accordance with literature values¹²

5.2.13 Potassium (*E*)-1,2-diphenyl-vinyl-trifluoroborate (2.123)

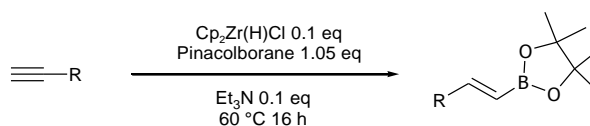


Biphenylacetylene (2.00 g, 11.22 mmol) was reacted under route B to afford the title compound as a light cream powder (0.749 g, 23% yield).

Mp; >250 °C; ν_{\max} (neat)/cm⁻¹; 3080, 3022 (C-H), 1621 (C=C); δ_{H} (300 MHz; acetone); 7.03 (4H, d, *J* 4.5 Hz, ArH), 6.92-6.81 (6H, m, ArH), 6.62 (1H, s, ArCH); δ_{C} (75.5 MHz; acetone); 147.6, 141.2, 129.9, 129.1, 128.1, 125.6, 124.8; δ_{B} (96 MHz; MeOD); 3.95; δ_{F} (471 MHz; MeOD); -145.3; HRMS (ESI⁻) *calcd* for [M]⁻ C₁₄H₁₁BF₃ *m/z* 247.0906 found: *m/z* 247.0903

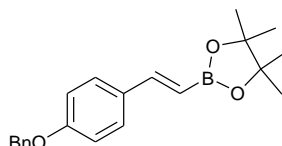
5.3 Synthesis of (*E*)-alkenyl 4,4,5,5-tetramethyl-[1,3,2]dioxaborolanes

5.3.1 General procedure for the synthesis of (*E*)-alkenyl 4,4,5,5-tetramethyl-[1,3,2]dioxaborolanes



Alkyne (4.00 g, 25.0 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.36 g, 26.3 mmol) were charged to a 25 mL Schlenk tube under a positive pressure of dry argon. To the resulting solution was added bis(cyclopentadienyl)zirconium(IV) chloride hydride (0.65 g, 2.5 mmol) followed by triethylamine (0.25 g, 2.5 mmol). The mixture was capped and then heated at 60 °C for 16 hours with protection from light. Upon completion, hexane (5 mL) was added and the mixture stirred for 10 minutes in air. The material was isolated through a short silica pad (elution: hexanes) and concentrated under reduced pressure to afford the desired (*E*)-alkenylboronic esters.

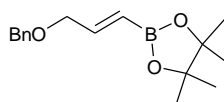
5.3.2 2-[2-(4-Benzyloxy-phenyl)-vinyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**2.131**)



Under the standard conditions 1-benzyloxy-4-ethynyl-benzene (**2.101**) (2.15 g, 10.32 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.65 mL, 11.35 mmol) to afford the title compound as a yellow solid (3.1 g, 89% yield).

Mp; 88-89 °C; ν_{max} (neat)/ cm^{-1} ; 2982, 2940 (C-H), 1627 (C=C), 1604, 1575 (aryl C=C), 1357, 1333 (B-O); δ_{H} (300 MHz; CDCl_3); 7.46-7.32 (8H, m, ArH, CH), 6.94 (2H, d, J 8.8 Hz, ArH), 6.02 (1H, d, J 18.4 Hz, CH), 5.07 (2H, s, OCH_2), 1.32 (12H, s, $(\text{CH}_3)_2\text{CC}(\text{CH}_3)_2$); δ_{C} (75.5 MHz; CDCl_3); 159.6, 149.1, 136.9, 130.7, 128.7, 128.6, 128.1, 127.5, 115.0, 83.3, 70.1, 24.9 (no C-B observed); δ_{B} (96 MHz; CDCl_3); 32.58; HRMS (ESI⁺) *calcd* for $\text{C}_{21}\text{H}_{25}\text{BNaO}_3$ [$\text{M}+\text{Na}$]⁺ m/z 359.1794 found: m/z 359.1809

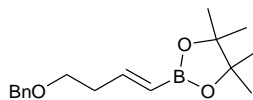
5.3.3 2-(3-Benzoyloxy-propenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (2.132)



Prop-2-ynyloxymethyl-benzene (**2.103**) (2.5 g, 17.1 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.73 mL, 18.81 mmol) under the standard conditions to afford the title compound as a yellow oil (4.59 g, 98% yield).

ν_{\max} (neat)/ cm^{-1} : 3028, 2980, 2902 (C-H), 1645 (C=C), 1360, 1326 (B-O); δ_{H} (300 MHz; CDCl_3): 7.37-7.27 (5H, m, ArH), 6.69 (1H, dt, J 18.2, 4.7 Hz, CHCHB), 5.77 (1H, dt, J 18.1, 1.8 Hz, CHCHB), 4.54 (2H, s, ArCH₂O), 4.11 (2H, dd, J 4.7, 1.8 Hz, CH₂CH), 1.27 (12H, s, (CH₃)₂CC(CH₃)₂); δ_{C} (75.5 MHz; CDCl_3): 149.2, 138.4, 128.4, 127.7, 127.6, 83.3, 72.4, 71.8, 24.8 (no C-B observed); δ_{B} (96 MHz; CDCl_3): 32.84; HRMS (ESI⁺) *calcd* for [M+H]⁺ C₁₆H₂₄BO₃ m/z 275.1819 found: m/z 275.1820

5.3.4 2-(4-Benzoyloxy-but-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (2.133)

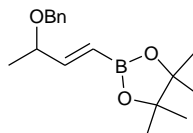


But-3-ynyloxymethyl-benzene (**2.104**) (3.5 g, 21.85 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.49 mL, 24.03 mmol) under the standard conditions to afford the title compound as a yellow oil (5.97 g, 95% yield).

ν_{\max} (neat)/ cm^{-1} : 2980, 2928 (C-H), 1640 (C=C), 1359, 1323 (B-O); δ_{H} (300 MHz; CDCl_3): 7.26-7.17 (5H, m, ArH), 6.56 (1H, dt, J 18.0, 6.4 Hz, CHCHB), 5.46 (1H, dt, J 18.0, 1.6 Hz, CHCHB), 4.44 (2H, s, ArCH₂O), 3.48 (2H, t, J 6.9 Hz, OCH₂CH₂), 2.41 (2H, qd, J 6.7, 1.6 Hz, CH₂CH), 1.19 (12H, s, (CH₃)₂CC(CH₃)₂); δ_{C} (75.5 MHz; CDCl_3): 150.5, 138.5, 128.4, 127.7, 127.6, 83.1, 73.0, 69.0, 36.2, 24.8 (no C-B observed); δ_{B} (96 MHz; CDCl_3): 31.65; HRMS (ESI⁺) *calcd* for C₁₇H₂₅BNaO₃ [M+Na]⁺ m/z 311.1794 found: m/z 311.1805

All data in accordance with literature values⁷

5.3.5 2-(3-Benzyloxy-but-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (2.134)

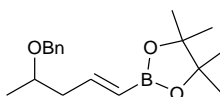


Under the standard conditions (1-methyl-prop-2-ynyloxymethyl)-benzene (**2.105**) (8.0 g, 49.9 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7.99 mL, 55.0 mmol) to afford the title compound as a yellow oil (13.7 g, 96% yield).

ν_{\max} (neat)/ cm^{-1} : 2979, 2932 (C-H), 1641 (C=C), 1359, 1326 (B-O); δ_{H} (300 MHz; CDCl_3); 7.29–7.15 (5H, m, ArH), 6.45 (1H, dd, J 18.1, 6.3 Hz, CHCHB), 5.57 (1H, dd, J 18.1, 1.1 Hz, CHCHB), 4.50 (1H, d, J 12.0 Hz, CHH), 4.31 (1H, d, J 12.0 Hz, CHH), 3.91 (1H, quintetd, J 6.5, 1.1 Hz, CH_3CH), 1.21 (12H, s, $(\text{CH}_3)_2\text{CC}(\text{CH}_3)_2$), 1.21 (3H, d, J 6.4 Hz, CH_3CH); δ_{C} (75.5 MHz; CDCl_3); 154.4, 138.8, 128.3, 127.7, 127.4, 83.4, 70.4, 24.8, 20.9 (no C-B observed); δ_{B} (96 MHz; CDCl_3); 34.64; HRMS (ESI⁺) *calcd* for $\text{C}_{17}\text{H}_{26}\text{BNaO}_3$ $[\text{M}+\text{Na}]^+$ m/z 289.1975 found: m/z 289.1981

All data in accordance with literature values⁷

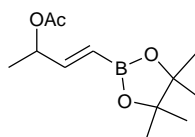
5.3.6 2-(4-Benzyloxy-pent-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (2.135)



Under the standard conditions (1-methyl-but-3-ynyloxymethyl)-benzene (**2.106**) (5.0 g, 29.03 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.63 mL, 31.93 mmol) to afford the title compound as a yellow oil (8.0 g, 92% yield).

ν_{\max} (neat)/ cm^{-1} : 3031, 2980, 2930, (C-H), 1607 (C=C), 1377, 1342 (B-O); δ_{H} (300 MHz; CDCl_3); 7.28 (5H, m, ArH), 6.6 (1H, dt, J 17.9, 6.9 Hz, CHCHB), 5.43 (1H, dt, J 17.9, 1.4 Hz, CHCH), 4.49–4.40 (2H, m, OCH_2Ar), 3.55 (1H, sextet, J 6.1 Hz, CH_3CH), 2.48–2.39 (1H, m, CHCHH), 2.30–2.20 (1H, m, CHCHH), 1.19 (12H, s, $(\text{CH}_3)_2\text{CC}(\text{CH}_3)_2$), 1.13 (3H, d, J 6.1 Hz, CH_3CH); δ_{C} (75.5 MHz; CDCl_3); 150.4, 139.0, 128.4, 127.7, 127.5, 83.1, 74.1, 70.4, 43.1, 24.9, 19.8 (no C-B observed); δ_{B} (96 MHz; CDCl_3); 34.64

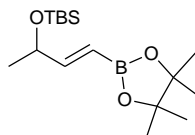
5.3.7 Acetic acid 1-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-allyl ester (2.136)



Acetic acid 1-methyl-prop-2-ynyl ester (**2.110**) (1.5 g, 12.2 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.96 mL, 13.5 mmol) under the standard conditions to afford the title compound as a colourless oil (1.9 g, 66% yield).

ν_{\max} (neat)/ cm^{-1} ; 2981, 2934 (C-H), 1739 (C=O), 1645 (C=C), 1360, 1326 (B-O); δ_{H} (300 MHz; CDCl_3); 6.54 (1H, dd, J 18.2, 4.7 Hz, CHCHB), 5.58 (1H, dd, J 18.2, 1.6 Hz, CHCHB), 5.44-5.34 (1H, m, CH_3CH), 2.05 (3H, s, COCH_3), 1.26 (12H, s, $(\text{CH}_3)_2\text{CC}(\text{CH}_3)_2$), 0.24 (3H, d, J 6.2 Hz, CHCH_3); δ_{C} (75.5 MHz; CDCl_3); 170.3, 151.3, 83.5, 71.3, 24.9, 21.3, 19.7 (no C-B observed); δ_{B} (96 MHz; CDCl_3); 32.78; HRMS (ESI^+) *calcd* for $[\text{M}+\text{Na}]^+$ $\text{C}_{12}\text{H}_{21}\text{BNaO}_4$ m/z 263.1431 found: m/z 263.1422

5.3.8 2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-but-1-enyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (2.137)

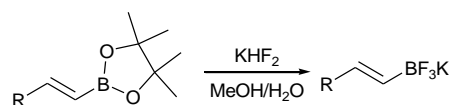


Under the standard conditions *tert*-butyl-dimethyl-(1-methyl-prop-2-ynyloxy)-silane (**2.111**) (1.1 g, 5.97 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.95 mL, 5.56 mmol) to afford the title compound as a yellow oil (1.27 g, 79% yield).

ν_{\max} (neat) / cm^{-1} ; 2980, 2931, 2859 (C-H), 1644 (C=C), 1367, 1345 (B-O); δ_{H} (300 MHz; CDCl_3); 6.59 (1H, dd, J 17.9, 3.9 Hz, CHCHB), 5.60 (1H, dd, J 17.9, 1.5 Hz, CHCHB), 4.35-4.31 (1H, m, CH_3CH), 1.27 (12H, s, $(\text{CH}_3)_2\text{CC}(\text{CH}_3)_2$), 1.21 (3H, d, J 6.5 Hz, CH_3CH), 0.90 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.04 (6H, s, $\text{Si}(\text{CH}_3)_2$); δ_{C} (75.5 MHz; CDCl_3); 157.1, 83.2, 69.9, 26.0, 24.9, 24.8, 23.8, -4.6, -4.8 (no C-B observed); δ_{B} (96 MHz; CDCl_3); 32.84; HRMS (ESI^+) *calcd* for $\text{C}_{16}\text{H}_{33}\text{BNaO}_3\text{Si}$ $[\text{M}+\text{Na}]^+$ m/z 335.2189 found: m/z 335.2174

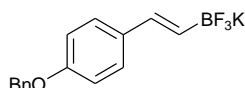
5.4 Synthesis of potassium alkenyl trifluoroborate salts

5.4.1 General procedure for the synthesis of potassium alkenyl trifluoroborate salts



Alkenyl boronic esters (27.76 mmol) were dissolved in MeOH (50 mL). KHF_2 (9.0 eq) was added in one portion followed by addition of water (20 mL). After stirring at room temperature for 0.5 h, the solution was concentrated *in vacuo*. Crude product was dissolved in acetone (20 mL), filtered and the filtrate evaporated to dryness. The resulting solid was purified by dissolving in minimum hot acetone and precipitating with diethyl ether in the freezer overnight, subsequently the solution was filtered to afford the products as solids.

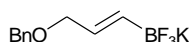
5.4.2 Potassium (*E*)-(4-(benzyloxy)styryl)trifluoroborate (**2.138**)



Under the standard conditions 2-[2-(4-benzyloxy-phenyl)-vinyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**2.131**) (2.74 g, 8.15 mmol) was reacted to afford the title compound as a white solid (1.03 g, 89% yield).

Mp; decomposes at 140 °C; ν_{max} (neat)/ cm^{-1} ; 3060, 3032, 2981, 1879 (C-H), 1650 (C=C); δ_{H} (300 MHz; DMSO); 7.46-7.29 (5H, m, ArH), 7.22 (2H, d, J 8.6 Hz, ArH), 6.89 (2H, d, J 8.6 Hz, ArH), 6.38 (1H, d, J 18.3 Hz, CHCHB), 5.99 (1H, dq, J 13.3, 3.5 Hz, CHCHB), 5.06 (2H, s, ArCH₂); δ_{C} (75.5 MHz; DMSO); 156.7, 152.3, 137.4, 128.4, 127.8, 127.7, 126.4, 114.6, 69.2 (C-B not observed); δ_{B} (96 MHz; MeOD); 3.55; δ_{F} (471 MHz; MeOD); -139.42

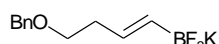
5.4.3 Potassium (*E*)-(3-(benzyloxy)prop-1-en-1-yl)trifluoroborate (**2.139**)



Under the standard conditions 2-(3-benzyloxy-propenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**2.132**) (4.21 g, 15.35 mmol) was reacted to afford the title compound as a white solid (2.883 g, 74% yield).

Mp; decomposes at 129 °C; ν_{\max} (neat)/cm⁻¹; 3060, 3032, 2981, 2879 (C-H), 1650 (C=C), 1073 (C-O); δ_{H} (300 MHz; MeOD), 7.10-7.00 (5H, m, ArH); 5.56 (1H, dt, *J* 12.2, 6.5 Hz, CHCHB), 5.22 (1H, dd, *J* 17.6, 3.8 Hz, CHCHB), 4.27 (2H, s, ArCH₂O), 2.16-2.07 (1H, m, CHCH₂O), 1.91-1.82 (1H, m, CHCH₂O); δ_{C} (75.5 MHz; MeOD); 140.2, 138.8, 129.3, 128.9, 128.5, 76.8, 71.4 (no C-B observed); δ_{B} (96 MHz; MeOD) 3.24; δ_{F} (471 MHz; MeOD); -142.7; HRMS (ESI) *calcd* for [M]⁻ C₁₀H₁₁BF₃O₁ *m/z* 215.0855 found: *m/z* 215.0848

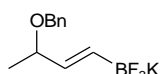
5.4.4 Potassium (*E*)-(4-(-benzyloxy)but-1-en-1-yl)trifluoroborate (2.140)



Under the standard conditions 2-(4-benzyloxy-but-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**2.133**) (5.0 g, 17.35 mmol) was reacted to afford the title compound as a white solid (4.4 g, 95% yield).

ν_{\max} (neat)/cm⁻¹; 3030, 2981, 2952, 2899, 2863 (C-H), 1645 (C=C); δ_{H} (500 MHz; MeOD); 7.33-7.31 (5H, m, ArH), 5.81 (1H, dt, *J* 17.6, 6.6 Hz, CHCHB), 5.49 (1H, dt, *J* 17.7, 3.4 Hz, CHCHB), 4.49 (2H, s, ArCH₂O), 3.51 (2H, t, *J* 7.1 Hz, OCH₂CH₂), 2.31 (2H, q, *J* 6.8 Hz, OCH₂CH₂); δ_{C} (126 MHz; MeOD); 152.1, 139.7, 129.3, 128.9, 128.6, 73.7, 71.6, 37.1 (C-B not observed); δ_{B} (160 MHz; MeOD); 3.22; δ_{F} (471 MHz; MeOD); -142.68

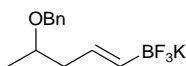
5.4.5 Potassium (*E*)-(3-phenoxybut-1-en-1-yl)trifluoroborate (2.141)



Under the standard conditions 2-(3-benzyloxy-but-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**2.134**) (8.0 g, 27.76 mmol) was reacted to afford the title compound as a white solid (6.0 g, 81% yield).

Mp; 90 °C; ν_{\max} (neat)/cm⁻¹; 3032, 2976, 2869 (C-H), 1644 (C=C); δ_{H} (500 MHz; CDCl₃); 7.33-7.29 (4H, m, ArH), 7.26-7.23 (1H, m, ArH), 5.74 (1H, dd, *J* 18.0, 7.3 Hz, CHCHB), 5.60 (1H, dq, *J* 18.0, 3.7 Hz, CHCHB), 4.56 (1H, d, *J* 11.9 Hz, ArCHH), 4.35 (1H, d, *J* 11.9 Hz, ArCHH), 3.84 (1H, quintet, *J* 6.6 Hz, CH₃CH), 1.22 (3H, d, *J* 6.4 Hz, CH₃CH); δ_{C} (126 MHz; MeOD); 140.3, 138.8, 129.2, 129.0, 128.4, 80.1, 70.6, 21.9 (C-B not observed); δ_{B} (160 MHz; MeOD); 3.09; δ_{F} (471 MHz; MeOD); -143.10

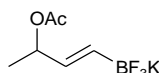
5.4.6 Potassium (*E*)-(4-(benzyloxy)pent-1-en-1-yl)trifluoroborate (2.142)



Under the standard conditions 2-(4-Benzyloxy-pent-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**2.135**) (5.0 g, 16.54 mmol) was reacted to afford the title compound as a white solid (1.6 g, 34% yield).

Mp; 140-141 °C; ν_{\max} (neat)/cm⁻¹; 2980, 2936 (C-H), 1647 (C=C); δ_{H} (300 MHz; MeOD); 7.34-7.25, (5H, m, ArH), 5.82 (1H, dt, *J* 16.9, 6.6 Hz, CHCHB), 5.48 (1H, dt, *J* 17.7, 3.6 Hz, CHCHB), 4.53 (2H, s, ArCH₂O), 3.58 (1H, sextet, *J* 6.0 Hz, CH₃CH), 2.41-2.36 (1H, m, CHCHHCH), 2.17-2.08 (1H, m, CHCHHCH), 1.18 (3H, d, *J* 6.1 Hz, CH₃CH); δ_{C} (75.5 MHz; CDCl₃); 140.2, 133.7, 129.3, 128.9, 128.5, 76.9, 71.4, 44.0, 19.9 (C-B not observed); δ_{B} (96 MHz; MeOD); 6.10; δ_{F} (471 MHz; MeOD); -142.80

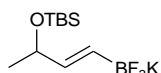
5.4.7 Potassium (*E*)-(3-(acetoxybut-1-en-1-yl)trifluoroborate (2.143)



Acetic acid 1-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-allyl ester (**2.136**) (1.9 g, 7.91 mmol) was reacted under the standard conditions to afford the title compound as a white solid (0.48 g, 28% yield).

ν_{\max} (neat)/cm⁻¹; 2980, 2932 (C-H), 1714 (C=O), 1651 (C=C); δ_{H} (300 MHz; MeOD); 5.78 (1H, dd, *J* 17.9, 5.8 Hz, CHCHB), 5.58 (1H, dqd, *J* 17.9, 3.7, 1.0 Hz, CHCHB), 5.22 (1H, quintet, *J* 6.1 Hz, CH₃CH), 2.01 (3H, s, COCH₃), 1.25 (3H, d, *J* 6.5 Hz, CH₃CH); δ_{C} (75.5 MHz; MeOD); 172.6, 136.6, 75.0, 21.4, 20.6 (C-B not observed); δ_{B} (96 MHz; MeOD); 6.23; δ_{F} (471 MHz; MeOD); -143.53; HRMS (ESI) *calcd* for C₆H₉BF₃O₂ [M]⁻ *m/z* 181.0648 found: *m/z* 181.0685

5.4.8 Potassium (*E*)-(3-((*tert*-butyldimethylsilyl)oxy)but-1-en-1-yl)trifluoroborate (2.144)

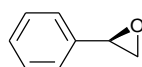


Under the standard conditions 2-[3-(*tert*-butyl-dimethyl-silanyloxy)-but-1-enyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**2.137**) (1.0 g, 3.7 mmol) was reacted to afford the title compound as a white solid (0.108 g, 10% yield).

Mp; decomposes at 170 °C; ν_{max} (neat)/cm⁻¹; 2959, 2930, 2857 (C-H), 1649 (C=C); δ_{H} (500 MHz; MeOD); 5.78 (1H, dd, *J* 17.6, 5.5 Hz, CHCHB), 5.48 (1H, dd, *J* 17.8, 3.8 Hz, CHCHB), 4.23 (1H, t, *J* 6.0 Hz, CH₃CH), 1.17 (3H, d, *J* 6.3 Hz, CH₃CH), 0.90 (9H, s, SiC(CH₃)₃), 0.06 (6H, s, Si(CH₃)₂); δ_{C} (126 MHz; MeOD); 152.2, 77.8, 26.5, 26.3, 24.9, -4.2, -4.6 (C-B not observed); δ_{B} (160 MHz; MeOD); 2.94; δ_{F} (471 MHz; MeOD); -143.17

5.5 Synthesis of enantiopure epoxides

5.5.1 (*R*)-2-phenyloxirane (2.172)



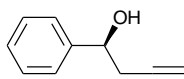
To a 50 mL round bottom flask was added (*R,R*)-N,N-Bis(3,5-*tert*-butylsalicylidene)-1,2-cyclohexdiaminecobalt (II) (0.628 g, 1.04 mmol). Dichloromethane (4 mL) and acetic acid (600 μ L) were added and the red solution stirred in air for 30 min. The resulting brown solution was concentrated *in vacuo* to give a brown residue. The active catalyst was dissolved in neat styrene oxide (25 g, 208 mmol) with anhydrous THF (4 mL) and the flask cooled to 0 °C (ice/water). Water was added dropwise (2.06 mL, 114.4 mmol, 0.55 eq), the mixture was capped with a greased glass stopper for 48 h at room temperature. After this time the reaction flask was attached to a short path distillation and the volatiles distilled under high vacuum (65 °C, 5mmHg).¹⁴ The recovered epoxide was passed through a short silica pad to remove residual water and THF to afford the title compound as a colourless oil (11.268 g, 92% yield out of maximum theoretical yield). The recovered epoxide was determined to be >99% ee by chiral HPLC analysis. (Diacel Chiracel OD-H, hexane/propan-2-ol (99:1), 0.4 mL min⁻¹, 220 nm, t_{R} (minor) = 38.59 min, t_{R} (major) = 40.38 min).

$[\alpha]_{\text{D}}^{20} = -24$ ($c=1.1$, CHCl₃); lit¹⁵ $[\alpha]_{\text{D}}^{20} = -24$ ($c=1.1$, CHCl₃); δ_{H} (300MHz, CDCl₃); 7.30-7.17 (5H, m, Ar), 3.72 (1H, dd, *J* 3.9, 2.5 Hz, CHCH₂), 3.06 (1H, dd, *J* 5.5, 4.0 Hz, CHCH₂), 2.72 (1H, dd, *J* 5.7, 2.6 Hz, CHCH₂), δ_{C} (75.5MHz, CDCl₃); 137.6, 128.5, 128.1, 125.5, 52.32, 51.1

All data in accordance with literature values¹⁴

5.6 Synthesis of enantiopure alkynes

5.6.1 (*S*)-1-Phenyl-but-3-yn-1-ol (2.173)

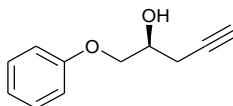


Lithium acetylide EDA complex (11.0 g, 109 mmol) was charged to a 100 mL round bottomed flask and suspended in anhydrous dimethylsulfoxide (45 mL). The resulting reaction mixture was immersed in a room temperature water bath. To the brown-black suspension was added (*R*)-styrene oxide (**2.172**) (5.00 g, 41.7 mmol) in one portion with vigorous stirring. The mixture was stirred for a further 2 hours at 23 °C. Upon completion the suspension was poured into 4 °C water (150 mL) and stirred for 30 minutes to quench excess acetylide. This was then filtered through a pad of Celite® washing with diethyl ether (3 x 100 mL). The combined washings were then extracted with water (2 x 100 mL), brine (2 x 150 mL), dried (NaSO₄) and concentrated. Final traces of DMSO and water were removed through a short silica pad to give the title product as golden yellow oils (5.482 g, 90% yield).

R_f (petrol/ethyl acetate, 9:1); 0.4; [α]_D²⁰ = +12.8 (*c*=1.10, CH₃OH); lit¹⁶ [α]_D²⁰ = +12.9 (CH₃OH), ν_{\max} (neat)/cm⁻¹; 3382 (O-H), 3295 (C-H Alkyne); δ_{H} (300 MHz; CDCl₃), 7.49-7.27 (5H, m, *Ph*), 4.86 (1H, t, *J* 6.4 Hz, *CHOCH*₂), 2.64 (2H, dd, *J* 6.4, 2.6 Hz, *CHOCH*₂), 2.43 (1H, br.s, *OH*), 2.07 (1H, t, *J* 2.6 Hz, *CH*₂*CCH*), δ_{C} (75.5 MHz; CDCl₃); 142.3, 128.4, 127.9, 125.6, 80.6, 72.2, 70.9, 29.3

All data in correspondence with literature values¹⁶

5.6.2 1-(*S*)-Phenoxy-pent-4-yn-2-ol (2.175)

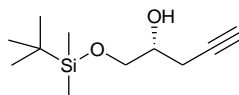


Lithium acetylide EDA complex (11.52 g, 125.1 mmol) was charged to a 100 mL round bottomed flask and suspended in anhydrous dimethylsulfoxide (70 mL). The resulting reaction mixture was immersed in a room temperature water bath. To the brown-black suspension was added (*S*)-2-oxyranylanisole (6.52 mL, 48.1 mmol) in one portion with vigorous stirring. The mixture was stirred for a further 4 hours at 23 °C. Upon

completion the suspension was poured into 4 °C solution of water and diethyl ether (5:2, 200 mL) then acidified to neutral by addition of 1M HCl solution. This was then filtered through a pad of Celite® washing with diethyl ether (3 x 100 mL). The combined washings were then extracted with water (2 x 100 mL), brine (2 x 150 mL), dried (NaSO₄) and concentrated. The crude product was purified by flash column chromatography on silica gel eluting with 9:1 hexane/ethyl acetate to give the title product as golden yellow oils (7.16 g, 85% yield).

R_f (petrol/ethyl acetate, 4:1); 0.1; $[\alpha]_D^{20} = +0.1$ ($c=1.26$, CHCl₃); ν_{\max} (neat)/cm⁻¹; 3421 (O-H), 3292 (C-H alkyne), 2120 (C≡C), 1495, 1457 (Ar C=C), 1241 (C-O aryl), 1117 (C-O alkyl); δ_H (300 MHz; CDCl₃), 7.25-7.18 (2H, m, Ar); 6.93-6.83 (3H, m, Ar), 4.15-4.07 (1H, m, CH₂CHCH₂), 4.03 (1H, dd, J 9.4, 4.0 Hz, PhOCHH), 3.94 (1H, dd, J 9.4, 6.4 Hz, PhOCHH), 2.51 (2H, dd, J 6.2, 2.7 Hz, CH₂CCH), 2.00 (1H, t, J 2.7 Hz, CH₂CCH); δ_C (75.5 MHz; CDCl₃); 171.6, 158.8, 130.0, 121.7, 115.2, 115.0, 80.2, 71.5, 70.8, 68.8, 24.0; HRMS (ESI⁺) *calcd* for C₁₁H₁₂NaO₂[M+Na]⁺ m/z 199.0735 found m/z 199.0717

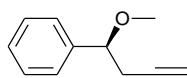
5.6.3 (*R*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-pent-4-yn-2-ol (2.176)



Lithium acetylide EDA complex (2.98 g, 32.38 mmol) was charged to a 100 mL round bottomed flask and suspended in anhydrous dimethylsulfoxide (25 mL). The resulting reaction mixture was immersed in a room temperature water bath. To the brown-black suspension was added (*R*)-*tert*-butyldimethylsilylglycidylether (3.0 mL, 12.45 mmol) in one portion with vigorous stirring. The mixture was stirred for a further 4 hours at 23 °C. Upon completion the suspension was poured into 4 °C solution of water and diethyl ether (5:2, 100 mL) then acidified to neutral by addition of 1M HCl solution. This was then filtered through a pad of Celite® washing with diethyl ether (3 x 100 mL). The combined washings were then extracted with water (2 x 100 mL), brine (2 x 150 mL), dried (NaSO₄) and concentrated. The crude product was purified by flash column chromatography eluting with 4:1 hexanes/ethyl acetate to give the title product as golden yellow oils (10.44 g, 78% yield).

R_f (petrol:ethyl acetate, 4:1) 0.9; $[\alpha]_D^{20} = -11$ ($c=1.00$, CHCl_3); ν_{\max} (neat)/ cm^{-1} ; 3385 (O-H), 2954, 2930, 2858 (C-H), 2160 ($\text{C}\equiv\text{C}$), 1250 (Si-CH₃), 1093 (Si-O), 1033 (C-O); δ_{H} (300 MHz; CDCl_3), 3.87 (1H, dddd, J 12.6, 9.8, 6.3, 3.5 Hz, OCH_2CH), 3.76 (1H, dd, J 11.2, 3.5 Hz, OCHH), 3.60 (1H, dd, J 11.3, 6.2 Hz, OCHH), 2.52 (2H, m, CHCH_2CCH), 2.20 (2H, br.s, OH, CH_2CCH), 0.92 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.09 (6H, s, H_3CSiCH_3); δ_{C} (75.5 MHz; CDCl_3); 103.9, 86.1, 70.1, 65.5, 26.0, 24.9, 16.4, -4.6; HRMS (ESI^+) *calcd* for $\text{C}_{11}\text{H}_{22}\text{NaO}_2\text{Si}$ $[\text{M}+\text{Na}]^+$ m/z 237.1287 found m/z 237.1276

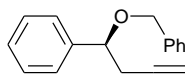
5.6.4 ((*S*)-1-Methoxy-but-3-ynyl)-benzene (2.177)



A 60% sodium hydride suspension in mineral oil (1.06 g, 44.1 mmol) was charged to a 250 mL round bottomed flask and suspended in anhydrous tetrahydrofuran (80 mL). The resulting mixture was cooled to 0 °C (ice/water) and to this was added (*S*)-1-phenyl-but-3-yn-1-ol (**2.173**) (4.38 g, 30.0 mmol) in one portion. The suspension was stirred for 30 minutes before methyl iodide (5.12 g, 36 mmol) was added dropwise. The mixture was allowed to warm to room temperature over 1 hour and then refluxed for a further 16 hours. Upon completion the suspension was concentrated in *vacuo*, and then resuspended in diethyl ether (100 mL). The organic phase was extracted with water (2 x 100 mL), brine (2 x 150 mL), dried (MgSO_4) and concentrated. Product was isolated by column chromatography (40:1 petrol/diethyl ether) to give the title compound as a colourless oil (4.61 g, 96% yield).

R_f (petrol/ethyl acetate, 40:1); 0.7; $[\alpha]_D^{20} = +12.4$ ($c=1.1$, CH_3OH); ν_{\max} (neat)/ cm^{-1} ; 3430 (C-H alkyne), 2930 (C-O), 2827 ($\text{C}\equiv\text{C}$); δ_{H} (300 MHz; CDCl_3), 7.29-7.10 (5H, m, *Ph*), 4.14 (1H, t, J 6.4 Hz, CHOCH_2), 3.06 (3H, s, OCH_3), 2.66 (1H, ddd, J 16.8, 6.4, 2.6 Hz, CHOCH_2), 2.47 (1H, ddd, J 16.8, 6.4, 2.6 Hz, CHOCH_2), 1.79 (1H, t, J 2.6 Hz, CH_2CCH); δ_{C} (75.5 MHz; CDCl_3); 140.3, 128.3, 127.9, 126.6, 81.8, 80.7, 69.8, 56.9, 27.8; HRMS (ESI^+) *calcd* for $\text{C}_{11}\text{H}_{12}\text{NaO}_1$ $[\text{M}+\text{Na}]^+$ m/z 160.0888 found: m/z 160.0886

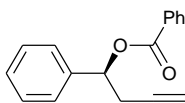
5.6.5 (*S*)-(1-Methoxy-but-3-ynyl)-benzene (**2.178**)



To a suspension of sodium hydride (0.3 g, 7.52 mmol) in THF (20 mL) at room temperature, was added dropwise a solution of (*S*)-1-phenyl-but-3-yn-1-ol (**2.173**) (1.1 g, 7.52 mmol) in THF (20 mL). The reaction mixture was stirred for 10 min before the addition of tetrabutylammonium iodide (2 crystals), followed by dropwise addition of benzylbromide (0.82 mL, 6.84 mmol) in THF (20 mL). The reaction was stirred overnight then diluted with water (50 mL), extracted with dichloromethane (4 x 50 mL) dried over magnesium sulphate, filtered and concentrated. The crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow oil (1.36 g, 84% yield).

R_f (petrol/ethyl acetate, 4:1); 0.52; $[\alpha]_D^{20} = -70$ ($c=1.00$, CHCl_3); ν_{max} (neat)/ cm^{-1} ; 3307 ($\equiv\text{C-H}$), 2915, 2837 (C-H), 2159 ($\text{C}\equiv\text{C}$), 1495, 1454 (aromatic C=C), 1090, 1070 (C-O); δ_{H} (300 MHz; CDCl_3), 7.40-7.29 (10 H, m, Ar), 4.52-4.5 (2H, m, ArCH_2O), 4.34 (1H, d, J 12.1 Hz, ArCHO), 2.77 (1H, ddd, J 16.6, 6.8, 2.6 Hz, CHCH_2C), 2.60 (1H, ddd, J 16.6, 6.6, 2.8 Hz, CHCH_2C), 1.97 (1H, t, J 2.6 Hz, CH_2CCH); δ_{C} (75.5 MHz; CDCl_3); 140.6, 138.1, 129.0, 128.8, 128.4, 128.3, 128.1, 127.7, 127.6, 126.9, 80.9, 79.3, 70.6, 70.0, 28.1; HRMS (ESI^+) *calcd* for $\text{C}_{17}\text{H}_{16}\text{NaO}$ $[\text{M}+\text{Na}]^+$ m/z 259.1099 found m/z 259.1083

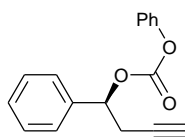
5.6.6 (*S*)-Benzoic acid 1-phenyl-but-3-ynyl ester (**2.179**)



To a stirred solution of (*S*)-1-phenyl-but-3-yn-1-ol (**2.173**) (1.0 g, 6.84 mmol) and pyridine (4.4 mL, 54.7 mmol) in dichloromethane (100 mL) was added dropwise benzoyl chloride (2.38 mL, 20.52 mmol) at 0 °C. Stirring was continued at 0 °C for 2.5 h. The reaction was diluted with saturated aqueous ammonium chloride (25 mL) and extracted with ethyl acetate (3 x 25 mL). Organic extracts were combined and washed with brine, dried (MgSO_4) and concentrated. The crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 20:1) to afford the title compound as a yellow oil (yield 1.32 g 77%).

R_f (petrol:ethyl acetate, 4:1); 0.57; $[\alpha]_D^{20} = +21$ ($c=1.00$, CHCl_3); ν_{max} (neat)/ cm^{-1} ; 3295 ($\equiv\text{C-H}$), 2160 ($\text{C}\equiv\text{C}$), 1717 (C=O), 1495, 1451 (aromatic C=C), 1264 (ester C-O), 1107 (ether C-O); δ_{H} (300 MHz; CDCl_3), 8.13-8.10 (2H, m, Ar), 7.58 (1H, tt, J 7.3, 1.6 Hz, Ar), 7.50-7.43 (4H, m, Ar), 7.42-7.30 (3H, m, Ar), 6.15 (1H, t, J 6.5 Hz, ArCHO), 2.95 (1H, ddd, J 16.8, 6.7, 2.7 Hz, CHCHHC), 2.86 (1H, ddd, J 16.8, 6.2, 2.6 Hz, CHCHHC), 1.99 (1H, t, J 2.6 Hz, CH_2CCH); δ_{C} (75.5 MHz; CDCl_3); 165.5, 139.0, 133.1, 130.1, 129.8, 128.5, 128.4, 128.4, 126.5, 79.4, 74.0, 70.9, 26.7; HRMS (ESI^+) *calcd* for $\text{C}_{17}\text{H}_{14}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ m/z 273.0891 found m/z 273.0885.

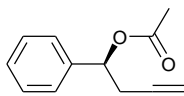
5.6.7 (*S*)-Carbonic acid phenyl ester 1-phenyl-but-3-ynyl ester (**2.180**)



To a stirred solution of (*S*)-1-phenyl-but-3-yn-1-ol (**2.173**) (1.0 g, 6.84 mmol) and pyridine (4.4 mL, 54.7 mmol) in dichloromethane (100 mL) was added dropwise phenyl chloroformate (2.58 mL, 20.52 mmol) at 0 °C. Stirring was continued at 0 °C for 2.5 h. The reaction was diluted with saturated aqueous ammonium chloride (25 mL) and extracted with ethyl acetate (3 x 25 mL). Organic extracts were combined and washed with brine, dried (MgSO_4) and concentrated. The crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 20:1) to afford the title compound as a white solid (1.4g, 76% yield).

R_f (petrol/ethyl acetate, 4:1); 0.57; $[\alpha]_D^{20} = -0.43$ ($c=1.00$, CHCl_3); ν_{max} (neat)/ cm^{-1} ; 3297 ($\equiv\text{C-H}$), 2161 ($\text{C}\equiv\text{C}$), 1770 (C=O), 1590, 1489, 1457 (aromatic C=C), 1252, 1230 (C-O); 1178, 1159 (C-O); 1072 (C-O); δ_{H} (300 MHz; CDCl_3), 7.49-7.31 (7H, m, Ar), 7.24-7.15 (3H, m, Ar), 5.84 (1H, t, J 6.7 Hz, ArCHCH_2), 2.95 (1H, ddd, J 16.8, 7.0, 2.7 Hz, CHCHHC), 2.83 (1H, ddd, J 16.8, 6.4, 2.7 Hz, CHCHHC), 2.05 (1H, t, J 2.7 Hz, CCH); δ_{C} (75.5 MHz; CDCl_3); 152.8, 151.1, 138.0, 129.4, 128.8, 128.6, 126.0, 121.0, 78.8, 78.3, 71.2, 26.6; HRMS (ESI^+) *calcd* for $\text{C}_{17}\text{H}_{14}\text{NaO}_3$ $[\text{M}+\text{Na}]^+$ m/z 289.0841 found m/z 289.0847

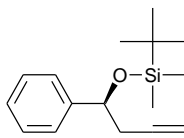
5.6.8 Acetic acid (*S*)-1-phenyl-but-3-ynyl ester (2.181)



In dichloromethane (12 mL), was dissolved (*S*)-1-phenyl-but-3-yn-1-ol (**2.173**) (1.00 g, 6.84 mmol). To the mixture was added 4-dimethylaminopyridine (0.418 g, 3.42 mmol) in one portion, followed by triethylamine (1.34 mL, 9.58 mmol) and acetic anhydride (0.78 mmol, 8.2 mmol). After stirring at room temperature for 2 h or until complete by TLC, the reaction mixture was poured into a separating funnel containing water (25 mL) and dichloromethane (25 mL). The organic phase was extracted and the aqueous phase extracted with dichloromethane (2 x 20 mL). Combined organic layers were washed with brine, dried over magnesium sulphate, filtered and concentrated. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a pale yellow oil (1.104 g, 86 % yield).

R_f (petrol:ethyl acetate, 4:1); 0.65; $[\alpha]_D^{20} = -83$ ($c=0.55$, CHCl_3); ν_{max} (neat)/ cm^{-1} ; 2160 ($\text{C}\equiv\text{C}$), 2032, 1977 (C-H), 1737 (C=O), 1215 (ester C-O), 1025 (ether C-O); δ_{H} (300 MHz; CDCl_3), 7.32-7.21 (5H, m, Ar), 5.83 (1H, t, J 6.6 Hz, ArCHO), 2.72 (1H, ddd, J 16.6, 6.8, 2.6 Hz, CHCHHC), 2.63 (1H, ddd, J 16.6, 6.4, 2.6 Hz, CHCHHC), 2.04 (3H, s, CH_3), 1.90 (1H, t, J 2.6 Hz, CCH); δ_{C} (75.5 MHz; CDCl_3); 170.0, 138.9, 128.4, 126.5, 126.5, 79.4, 73.5, 70.6, 26.4, 21.1; HRMS (ESI^+) *calcd* for $\text{C}_{12}\text{H}_{12}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ m/z 211.0735 found m/z 211.0725

5.6.9 *tert*-Butyl-dimethyl-((*S*)-1-phenyl-but-3-ynyloxy)-silane (2.182)

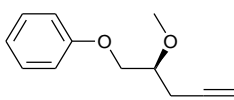


To a 100 mL round bottomed flask was charged (*S*)-1-phenyl-but-3-yn-1-ol (**2.173**) (2.51 g, 15.0 mmol) and anhydrous dimethylformamide (60 mL) added. To the resulting solution was added sequentially *tert*-butylchlorodimethylsilane (2.71 g, 18.0 mmol) followed by imidazole (3.06 g, 45.0 mmol), the mixture was then heated at 65 °C for 16 h. Upon completion the solution was poured into 4 °C water (150 mL) and stirred for 30 minutes. Ethyl acetate (100 mL) was added and the organic phase extracted with water

(2 x 100 mL), brine (2 x 100 mL), dried (MgSO₄) and concentrated. The material was isolated by column chromatography (petrol/diethyl ether, 40:1) to give the title product as a light yellow oil (3.59 g, 92% yield).

R_f (petrol: diethyl ether, 40:1); 0.7; $[\alpha]_D^{20} = +34.1$ (*c*=1.15, CH₃OH); ν_{\max} (neat)/cm⁻¹; 3309 (C-H alkyne), 2956, 2930, 2886, (C-O), 2858 (C≡C), 1097, 838.1 (O-Si); δ_H (500 MHz; C₆D₆), 7.35 (2H, d, *J* 7.3 Hz, Ph), 7.24 (2H, d, *J* 7.3 Hz, Ph), 7.15 (1H, t, *J* 7.3 Hz, Ph), 4.86 (1H, dd, *J* 7.3, 5.4 Hz, CHOCH₂), 2.63 (1H, ddd, *J* 16.7, 7.3, 2.8 Hz, CHOCH₂), 2.48 (1H, ddd, *J* 16.7, 5.4, 2.8 Hz, CHOCH₂), 1.83 (1H, t, *J* 2.8 Hz, CH₂CCH), 1.07 (9H, s, Si(CH₃)CCH₃), 0.19 (3H, s, Si(CH₃)C(CH₃)₃), 0.02 (3H, s, Si(CH₃)C(CH₃)₃); δ_C (125.2 MHz; C₆D₆); 144.1, 127.9, 128.0, 125.9, 81.5, 74.5, 74.0, 70.2, 31.6, 31.0, 25.8, 18.2, -4.61, -4.8, -5.01, -5.2; HRMS (ESI⁺) *calcd* for C₁₆H₂₄NaO₁Si₁ [M+Na]⁺ *m/z* 260.1596 found: *m/z* 260.1592.

5.6.10 (*S*)-(2-Methoxy-pent-4-ynyloxy)-benzene (2.183)

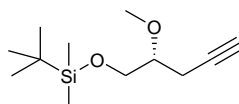


A 60% sodium hydride suspension in mineral oil (0.82 g, 20.45 mmol) was charged to a 250 mL round bottomed flask and suspended in anhydrous tetrahydrofuran (100 mL). The resulting mixture was cooled to 0 °C (ice/water) and to this was added (*S*)-1-phenoxy-pent-4-yn-2-ol (**2.175**) (3.0 g, 17.04 mmol) in one portion. The suspension was stirred for 30 minutes before methyl iodide (5.12 g, 36 mmol) was added dropwise. The mixture was allowed to warm to room temperature over 1 hour and then refluxed for a further 16 hours. Upon completion the suspension was concentrated in *vacuo*, and then dissolved in ethyl acetate (100 mL). The organic phase was extracted with water (2 x 100 mL), brine (2 x 150 mL), dried (MgSO₄) and concentrated. Product was isolated by column chromatography (petrol/ethyl acetate 9:1) to give the title compound as a colourless oil (2.4 g, 74% yield).

R_f (petrol:ethyl acetate, 4:1); 0.7; $[\alpha]_D^{20} = +10$ (*c*=1.00, CHCl₃); ν_{\max} (neat)/cm⁻¹; 3292 (≡C-H), 2931, 2828 (C-H), 2161 (C≡C), 1496, 1456 (Ar C=C), 1242 (Ar C-O), 1117 (C-O); δ_H (300 MHz; CDCl₃); 7.32-7.27 (2H, m, Ar), 6.99-6.93 (3H, m, Ar), 4.12 (2H, dd, *J* 4.8, 5.1 Hz, ArOCH₂), 3.74 (1H, quin. *J* 5.3 Hz, CH₂CHCH₂), 3.52 (3H, s, OCH₃), 2.64 (1H, ddd, *J* 17.0, 6.3, 2.6 Hz, CHCHH), 2.57 (1H, ddd, *J* 17.0, 5.5, 2.7 Hz,

CHCHH), 2.03 (1H, t, J 2.6 Hz, CH₂CCH); δ_C (75.5 MHz; CDCl₃); 158.6, 129.4, 121.0, 114.6, 80.2, 77.7, 70.3, 68.4, 57.9, 21.0; HRMS (ESI⁺) *calcd* for C₁₂H₁₄NaO₂ [M+Na]⁺ m/z 213.0891 found m/z 213.0893

5.6.11 (*R*)-*tert*-Butyl-(2-methoxy-pent-4-ynyloxy)-dimethyl-silane (2.184)

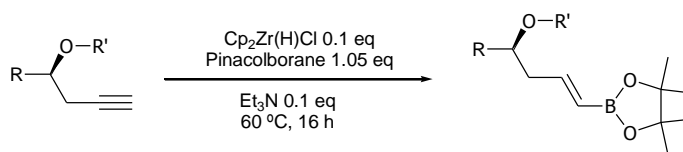


A 60% sodium hydride suspension in mineral oil (0.158 g, 3.96 mmol) was charged to a 250 mL round bottomed flask and suspended in anhydrous tetrahydrofuran (70 mL). The resulting mixture was cooled to 0 °C (ice/water) and to this was added (*R*)-1-(*tert*-butyl-dimethyl-silanyloxy)-pent-4-yn-2-ol (**2.176**) (0.72 g, 3.297 mmol) in one portion, the suspension was stirred for 30 minutes before methyl iodide (0.25 mL, 3.96 mmol) was added dropwise. The mixture was allowed to warm to room temperature over 1 hour and then refluxed for a further 16 hours. Upon completion the suspension was concentrated in *vacuo*, and then dissolved in ethyl acetate (25 mL). The organic phase was extracted with water (2 x 100 mL), brine (2 x 150 mL), dried (MgSO₄) and concentrated. Product was isolated by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to give the title compound as a yellow oil (0.47 g, 62% yield).

R_f (petrol/ethyl acetate, 4:1); 0.8; $[\alpha]_D^{20} = -6.25$ ($c=0.8$, CHCl₃); ν_{\max} (neat)/cm⁻¹; 3313 (\equiv C-H), 2926, 2855 (C-H), 2160 (C \equiv C), 1259 (Si-CH₃), 1102 (C-O), 1007 (Si-O); δ_H (300 MHz; CDCl₃); 3.63 (2H, d, J 5.3 Hz, OCH₂CH), 3.38 (3H, s, OCH₃), 3.31 (1H, app.t, J 6.0 Hz, CH₃OCH), 2.44 (1H, ddd, J 16.9, 5.9, 2.7 Hz, CCHH), 2.34 (1H, ddd, J 16.9, 5.4, 2.8 Hz, CHCHH), 1.91 (1H, app.t, J 2.7 Hz, CH₂CCH); δ_C (75.5 MHz; CDCl₃); 79.9, 79.0, 76.2, 68.6, 62.6, 56.8, 25.1, 24.9, 24.8, 19.6, 0.0, -6.4, -6.4; HRMS (ESI⁺) *calcd* for C₁₂H₂₄NaO₂Si [M+Na]⁺ m/z 251.1443 found m/z 251.1433

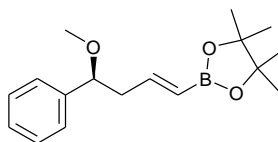
5.7 Synthesis of enantiopure (*E*)-alkenyl 4,4,5,5-tetramethyl-[1,3,2]dioxaborolanes

5.7.1 General procedure for the synthesis of enantiopure (*E*)-alkenyl 4,4,5,5-tetramethyl-[1,3,2]dioxaborolanes



The enantiopure alkyne (25.0 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.36 g, 26.3 mmol) were charged to a 25 mL Schlenk tube under a positive pressure of dry argon. To the resulting solution was added sequentially bis(cyclopentadienyl)zirconium(IV) chloride hydride (0.65 g, 2.5 mmol) followed by triethylamine (0.25 g, 2.5 mmol), the mixture was capped then heated at 60 °C for 16 hours with protection from light. Upon completion, hexane (5 mL) was added and the mixture stirred for 10 minutes in air. The material was isolated through a short silica pad and concentrated *in vacuo* to afford the desired enantiopure (*E*)-alkenyl 4,4,5,5-tetramethyl-[1,3,2]dioxaborolanes without the need for further purification.

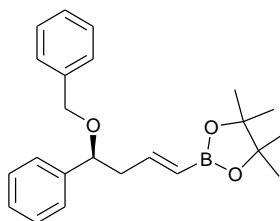
5.7.2 2-((*E*)-(*S*)-4-Methoxy-4-phenyl-but-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (2.185)



Under the general conditions ((*S*)-1-methoxy-but-3-ynyl)-benzene (**2.177**) (4.00 g, 25.0 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.36 g, 26.3 mmol). The material was isolated through a short silica pad (elution: hexanes) to give the title product as a colourless oil (5.83 g, 81% yield).

R_f (petrol/ethyl acetate, 9:1); 0.15; $[\alpha]_D^{20} = +12.9$ ($c=0.95$, CH_3OH); ν_{max} (neat)/ cm^{-1} ; 2980, 2931 (C=C), 1640 (C-O), 1358, 1323 (B-O); δ_H (300 MHz; CDCl_3); 6.62-6.48 (5H, m, Ph), 6.55 (1H, dt, J 19.6, 6.4 Hz CH alkene), 5.43 (1H, dt, J 19.6, 1.5 Hz CH alkene), 4.15 (1H, dd, J 8.3, 5.3 Hz, CHOCH_3), 3.1 (3H, s, OCH_3), 2.59 (1H, ddt, J 15.1, 6.4, 1.5 Hz, CHCH_2CHCH), 2.40 (1H, ddt, J 15.1, 8.3, 1.5 Hz, CHCH_2CHCH), 1.18 (12H, s, $(\text{CH}_3)_4$); δ_C (75.5 MHz; CDCl_3); 150.1, 141.7, 128.3, 127.5, 126.6, 83.0, 82.9, 56.6, 44.5, 24.7, C-B peak not observed; δ_B (96.3 MHz; CDCl_3); 31.2 Hz; HRMS (ESI^+) *calcd* for $\text{C}_{17}\text{H}_{25}\text{B}_1\text{Na}_1\text{O}_3$ $[\text{M}+\text{Na}]^+$ m/z 311.1794 found m/z 311.1791

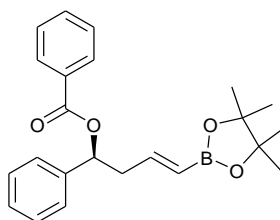
5.7.3 (S,E)-2-(4-Benzyloxy-4-phenyl-but-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (2.186)



Under the general conditions, (*S*)-(1-methoxy-but-3-ynyl)-benzene (**2.178**) (1.26 g, 5.35 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.85 mL, 5.88 mmol). The material was isolated through a short silica pad (elution: hexane/ethyl acetate 9:1) to give the title product as an orange oil (1.41 g, 72% yield).

R_f (petrol:ethyl acetate, 9:1); 0.9; $[\alpha]_D^{20} = -51$ ($c=1.07$, CHCl_3); ν_{max} (neat)/ cm^{-1} ; 2160, 2032 (C-H), 1639 (C=C), 1454 (aromatic C=C), 1363, 1322 (B-O), 1144, 1072 (C-O); δ_{H} (300 MHz; CDCl_3), 7.37-7.28 (10H, m, Ar), 6.62 (1H, dt, J 17.7, 6.6 Hz, *CHCHB*), 5.49 (1H, dt, J 17.7, 1.5 Hz, *CHCHB*), 4.45 (1H, d, J 11.7 Hz, *OCHHAr*), 4.42 (1H, dd, J 8.3, 5.3 Hz, *ArCHCH2*), 4.28 (1H, d, J 11.7, *OCHHAr*), 2.74 (1H, dddd, J 16.2, 8.3, 6.8, 1.5 Hz, *CHCHH*), 2.53 (1H, dddd, J 14.7, 6.4, 5.3, 1.5 Hz, *CHCHH*), 1.26 (12H, s, $(\text{CH}_3)_2\text{CC}(\text{CH}_3)_2$); δ_{C} (75.5 MHz; CDCl_3); 150.2, 141.9, 138.5, 128.4, 128.3, 127.6, 127.4, 126.8, 83.0, 80.6, 70.3, 24.8; δ_{B} (160.5 MHz; CDCl_3); 30.24 Hz; HRMS (ESI^+) *calcd* for $\text{C}_{23}\text{H}_{29}\text{BNaO}_3$ $[\text{M}+\text{Na}]^+$ m/z 387.2107 m/z found 387.2109

5.7.4 (S,E)-Benzoic acid 1-phenyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-but-3-enyl ester (2.187)

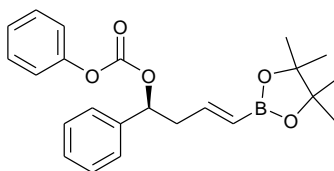


Under the general conditions, (*S*)-benzoic acid 1-phenyl-but-3-ynyl ester (**2.179**) (1.2 g, 4.79 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.76 mL, 5.27 mmol). The material was isolated through a short silica pad (elution: hexane/ethyl acetate 9:1) to give the title product as an orange oil (1.35 g, 75% yield).

R_f (petrol/ethyl acetate, 9:1); 0.9; $[\alpha]_D^{20} = -5$ ($c=1.00$, CHCl_3); ν_{max} (neat)/ cm^{-1} ; 2160, 2030, 1976 (C-H), 1716 (C=O), 1640 (C=C), 1362, 1324 (B-O), 1144 (ester C-O), 1070 (ether C-O); δ_{H} (300 MHz; CDCl_3), Rotamers 1:2; 8.09-8.05 (2H, m, Ar), 7.58-7.53

(1H, m, Ar), 7.46-7.28 (7H, m, Ar), 6.60 (1H, dt, J 18.1, 6.8 Hz, CHCHB), 6.05 (1H, dd, J 8.1, 5.5 Hz, CHCHB), 5.56 (1H, dtt, J 18.1, 8.9, 1.5 Hz, ArCHCH₂), 2.94 (1H, dddd, J 16.2, 8.3, 6.5, 1.5 Hz, CHCHH), 2.77 (1H, dddd, J 14.7, 6.7, 5.5, 1.5 Hz, CHCHH), 1.23 (12H, s, (CH₃)₂CC(CH₃)₂); δ_C (75.5 MHz; CDCl₃); 165.7, 148.2, 140.2, 132.9, 129.7, 128.5, 128.3, 128.0, 126.7, 126.4, 125.7, 83.1, 75.5, 24.7; δ_B (160.5 MHz; CDCl₃); 23.54; HRMS (ESI⁺) *calcd* for C₂₃H₂₇BNaO₄ [M+Na]⁺ m/z 401.1900 found: m/z 401.1894

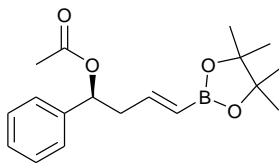
5.7.5 (*S,E*)-Carbonic acid phenyl ester 1-phenyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-but-3-enyl ester (2.188)



Under the standard conditions, (*S*)-carbonic acid phenyl ester 1-phenyl-but-3-ynyl ester (**2.180**) (1.97 g, 7.1 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.24 mL, 7.75 mmol). The material was isolated through a short silica pad (elution: hexane/ethyl acetate 9:1) to give the title product as an orange oil (2.57 g, 93% yield).

R_f (petrol/ethyl acetate, 9:1); 0.9; $[\alpha]_D^{20} = -19$ ($c=1.00$, CHCl₃); ν_{\max} (neat)/cm⁻¹; 2159, 2031, 1977 (C-H), 1764 (C=O), 1640 (C=C), 1454, 1473 (aromatic C=C), 1361, 1326 (B-O), 1247, 1210 (ester C-O), 1166, 1142 (ester C-O), 1070 (ether C-O); δ_H (300 MHz; CDCl₃); 7.39-7.30 (4H, m, Ar), 7.23-7.20 (2H, m, Ar), 7.15-7.11 (1H, m, Ar), 6.94-6.88 (1H, m, Ar), 6.85-6.81 (2H, m, Ar), 5.57-5.55 (1H, br. m, CHCHB), 5.20 (1H, br.s, CHCHB), 3.77 (1H, dd, J 6.6, 6.8 Hz, ArCHCH₂), 2.90 (1H, dddd, J 16.1, 8.1, 6.9, 1.4 Hz, CHCHH), 2.73 (1H, dddd, J 14.9, 6.6, 5.5, 1.5 Hz, CHCHH), 1.27 (12H, s, (CH₃)₂CC(CH₃)₂); δ_C (75.5 MHz; CDCl₃); 155.8, 129.6, 129.3, 128.6, 128.1, 126.1, 126.5, 125.8, 121.0, 120.5, 115.3, 83.2, 67.9, 24.5; δ_B (160.5 MHz; CDCl₃); 23.15 Hz; HRMS (ESI⁺) *calcd* for C₂₃H₂₇BNaO₅ [M+Na]⁺ m/z 417.1849 found m/z 417.1848

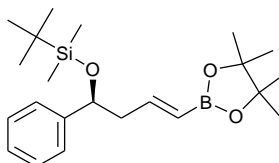
5.7.6 (*S,E*)-Acetic acid 1-phenyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-but-3-enyl ester (2.189)



Under the standard conditions (*S*)-acetic acid 1-phenyl-but-3-ynyl ester (**2.181**) (1.0 g, 5.3 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.85 mL, 5.83 mmol). The material was isolated through a short silica pad (elution: hexanes/ethyl acetate 9:1) to give the title product as an orange oil (1.43 g, 85% yield).

R_f (petrol/ethyl acetate, 9:1); 0.9; $[\alpha]_D^{20} = -35$ ($c=1.00$, CHCl_3); ν_{max} (neat)/ cm^{-1} ; 2979 (C-H), 1736 (C=O), 1639 (C=C), 1495, 1472, 1455 (ArC-H), 1360, 1323 (B-O), 1232 (ester C-O), 1143 (ether C-O); 300MHz, CDCl_3 : 7.37-7.28 (5H, m, Ar), 6.51 (1H, dt, J 17.9, 6.7 Hz, CHCHB), 5.82 (1H, dd, J 8.0, 5.5 Hz, CHCHB), 5.50 (1H, dt, J 17.9, 1.5 Hz, ArCH), 2.82 (1H, m, CHHCHCH), 2.63 (1H, m, CHHCHCH), 2.06 (3H, s, CH_3), 1.25 (12H, s, $(\text{CH}_3)_2\text{CC}(\text{CH}_3)_2$); δ_C (75.5 MHz; CDCl_3); 170.2, 148.2, 140.2, 128.4, 128.4, 127.9, 126.5, 126.5, 125.8, 83.2, 74.8 42.6, 24.7, 21.2; δ_B (160.5 MHz; CDCl_3); 28.73; HRMS (ESI^+) *calcd* for $\text{C}_{18}\text{H}_{25}\text{BNaO}_4$ $[\text{M}+\text{Na}]^+$ m/z 339.1743 found m/z 339.1744

5.7.7 2-[(*E*)-(*S*)-4-(*tert*-Butyl-dimethyl-silynyloxy)-4-phenyl-but-1-enyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (2.190)

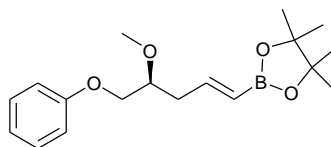


Under the standard conditions, *tert*-butyl-dimethyl-((*S*)-1-phenyl-but-3-ynyloxy)-silane (**2.182**) (2.60 g, 10.0 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.35 g, 10.5 mmol). The material was isolated through a short silica pad (elution: hexanes) to give the title product as a light yellow oil (2.80 g, 72% yield).

R_f (petrol/ethyl acetate, 9:1); 0.30; $[\alpha]_D^{20} = +37.2$ ($c=1.0$, CHCl_3); ν_{max} (neat)/ cm^{-1} ; 2978, 2957, 2930 (C=C), 1640 (C-O), 1363, 1322 (B-O), 849, 837 (O-Si); δ_H (300 MHz; CDCl_3); 7.47-7.41 (5H, m, *Ph*), 6.78 (1H, dt, J 18.1, 7.2 Hz CH alkene), 5.60 (1H, dt, J 18.1, 1.5 Hz CH alkene), 4.84 (1H, dd, J 7.9, 4.5 Hz, CHOCH_3), 2.74-2.52 (2H, m, CHCH_2CHCH), 1.39 (12H, s, $(\text{CH}_3)_4$), 1.04 (9H, s, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 0.14

(3H, s, OSi(CH₃)₂C(CH₃)₃), 0.00 (3H, s, OSi(CH₃)₂C(CH₃)₃); δ_C (75.5 MHz; CDCl₃); 151.1, 145.1, 128.0, 127.9, 126.9, 125.8, 125.7, 82.9, 74.7, 47.7, 25.8, 25.8, 24.7, 24.6, 18.2, -4.6, -4.9, C-B peak not observed; δ_B (96.3 MHz; CDCl₃); 28.3 Hz; HRMS (ESI⁺) *calcd* for C₁₇H₃₇BiNa₁O₃Si₁ [M+Na]⁺ *m/z* 411.2503 found *m/z* 411.2518.

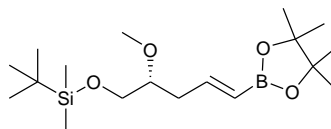
5.7.8 (*S,E*)-2-(4-Methoxy-4-phenoxy-but-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (2.191)



Under the general conditions (*S*)-(2-methoxy-pent-4-ynyloxy)-benzene (**2.183**) (2.14 g, 11.25 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.79 mL, 12.37 mmol). The material was isolated through a short silica pad (elution: hexanes/ethyl acetate 9:1) to give the title product as an orange oil (3.387 g, 95% yield).

R_f (petrol/ethyl acetate, 9:1); 0.1; $[\alpha]_D^{20} = +10$ ($c=1.00$, CHCl₃); ν_{max} (neat)/cm⁻¹; 2977, 2929 (C-H), 1639 (C=C), 1497, 1454 (aromatic C=C), 1357, 1321 (B-O), 1243 (C-O aromatic ether), 1143 (ether C-O); δ_H (300 MHz; CDCl₃); 7.30-7.24 (2H, m, Ar); 6.97-6.88 (4H, m, Ar), 6.65 (1H, dt, *J* 18.1, 6.8 Hz, CHCHB), 5.56 (1H, dt, *J* 18.1, 1.5 Hz, CHCHB), 3.98 (2H, d, *J* 5.28 Hz, ArCH₂CH), 3.68 (1H, ddd, *J* 11.3, 6.0, 5.0 Hz, CH₂CHCH₂), 3.47 (3H, s, OCH₃), 2.53 (2H, ddd, *J* 7.7, 6.2, 1.5 Hz, CHCH₂CHCH), 1.26 (12H, s, (CH₃)₂CC(CH₃)₂); δ_C (75.5 MHz; CDCl₃); 158.7, 149.2, 129.4, 120.8, 114.6, 83.1, 78.6, 69.2, 57.6, 37.7, 24.8; δ_B (160.5 MHz; CDCl₃); 28.98; HRMS (ESI⁺) *calcd* for C₁₈H₂₈BO₄ [M+H]⁺ *m/z* 319.2081 found *m/z* 319.2084

5.7.9 (*R,E*)-2-[5-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-pent-1-enyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (2.192)

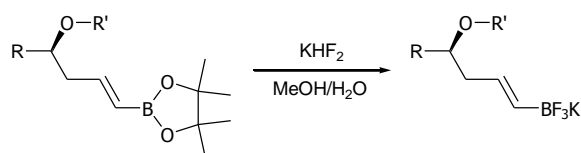


Under the general conditions (*R*)-*tert*-butyl-(2-methoxy-pent-4-ynyloxy)-dimethylsilane (**2.184**) (0.41 g, 1.795 mmol) was reacted with 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.28 mL, 1.97 mmol). The material was isolated through a short silica pad (elution: hexane/ethyl acetate 9:1) to give the title product as an orange oil (0.45 g, 70% yield).

R_f (petrol/ethyl acetate, 9:1); 0.1; $[\alpha]_D^{20} = -11.8$ ($c=0.85$, CHCl_3); ν_{max} (neat)/ cm^{-1} ; 2955, 2923, 2857 (C-H), 1640 (C=C), 1361, 1322 (B-O), 1252 (Si-CH₃), 1145, 1103 (C-O), 1007 (Si-O); δ_{H} (300 MHz; CDCl_3); 6.64 (1H, dt, J 17.7, 6.9 Hz, CHCHB), 5.50 (1H, dt, J 17.9, 1.5 Hz, CHCHB), 3.59 (2H, dd, J 10.6, 5.4 Hz, $\text{OCH}_2\text{CHCH}_2$), 3.40 (3H, s, OCH_3), 3.35-3.39 (1H, m, OCH_2CH), 2.33-2.42 (2H, m, CHCH_2CHCH), 1.3 (12H, s, $(\text{CH}_3)_2\text{CC}(\text{CH}_3)_2$), 0.89 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.07 (3H, s, SiCH_3), 0.05 (3H, s, SiCH_3); δ_{C} (75.5 MHz; CDCl_3); 149.3, 133.0, 82.0, 80.1, 63.6, 56.7, 28.7, 24.9, 24.6, 23.9, 23.8, 23.6, 0.0, -6.4; δ_{B} (160.5 MHz; CDCl_3); 23.47; HRMS (ESI^+) *calcd* for $\text{C}_{18}\text{H}_{37}\text{BNaO}_4\text{Si}$ $[\text{M}+\text{Na}]^+$ m/z 379.2460 found m/z 379.2456.

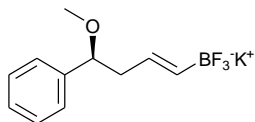
5.8 Synthesis of enantiopure potassium (*E*)-alkenyl trifluoroborate salts

5.8.1 General Procedure for the synthesis of enantiopure potassium (*E*)-alkenyl trifluoroborate salts



Enantiopure (*E*)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolanes (8.0 mmol) were charged to a 100 mL round bottom flask and methanol (25 mL) added. The flask was cooled to 0 °C and to the resulting solution was added sequentially potassium hydrogen difluoride (2.34 g, 30 mmol) followed by water (5 mL). The mixture was warmed to room temperature and stirred for 30 min until a heavy white precipitate forms. Upon completion the reaction mixture is concentrated *in vacuo* and thoroughly dried under high vacuum (0.01 mmHg). The solids were washed with copious acetone (250 mL) and filtered to remove inorganic salts. The solvent was concentrated *in vacuo* and the crude product recrystallised from hot acetone/diethyl ether. Storage overnight in a -20 °C freezer gave the desired products as white solids.

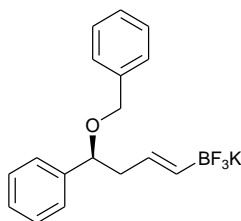
5.8.2 Potassium (*S,E*)-4-methoxy-4-phenylbut-1-enyl trifluoroborate (2.193)



Under the general conditions 2-((*E*)-(*S*)-4-methoxy-4-phenylbut-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**2.185**) (2.31 g, 8.0 mmol) was reacted with potassium hydrogen difluoride (2.34 g, 30 mmol) to afford the title compound as a white solid (1.97 g, 92% yield).

Mp; decomposed at 185 °C; $[\alpha]_D^{20} = +13.4$ ($c = 0.65$, MeOH); ν_{\max} (neat)/cm⁻¹; 2992, 2931 (C=C), 1652 (C-O), 1107, 946 (B-F); δ_H (300 MHz; CD₃OD); 8.32-8.15 (5H, m, Ph), 6.69 (1H, dt, J 17.7, 6.8 Hz *CH* alkene), 6.39 (1H, dt, J 17.7, 3.8 Hz *CH* alkene), 5.10 (1H, dd, J 7.5, 6.0 Hz, *CHOCH*₃), 4.12 (3H, s, *OCH*₃), 3.44 (1H, ddt, J 15.5, 6.4, 1.5 Hz, *CHCH*₂*CHCH*), 3.44 (1H, ddt, J 15.5, 7.5, 1.5 Hz, *CHCH*₂*CHCH*); δ_C (75.5 MHz; CD₃OD); 143.5, 133.7, 133.7, 129.3, 128.5, 127.9, 86.0, 56.7, 45.7, (C-B peak not observed); δ_B (96.3 MHz; CD₃OD); 4.12; δ_F (377 MHz; CD₃OD); -142.54; HRMS (ESI) *calcd* for C₁₁H₁₄B₁F₃O₁ [M]⁻ m/z 229.1011 found m/z 229.1009

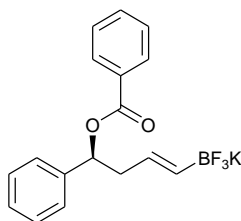
5.8.3 Potassium (*S,E*)-2-(4-benzyloxy-4-phenylbut-1-enyl) trifluoroborate (2.194)



Under the general conditions (*S,E*)-2-(4-benzyloxy-4-phenylbut-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**2.186**) (1.24 g, 3.4 mmol) was reacted with potassium hydrogen difluoride (2.39 g, 30.63 mmol) to afford the title compound as a white solid (1.41 g, 72% yield).

Mp; 150-152 °C; $[\alpha]_D^{20} = -43$ ($c=1.00$, MeOH); ν_{\max} (neat)/cm⁻¹; 1647 (C=C); 1492, 1453 (aromatic C=C), 1140, 1072 (C-O), 1059, 1026, 963 (B-F); δ_H (300 MHz; MeOH); 7.18-7.03 (10H, m, Ar), 5.58 (1H, dtd, J 17.7, 6.6, 1.3 Hz, *CHCHB*), 5.24 (1H, dqt, J 17.7, 3.9, 1.3 Hz, *CHCHB*), 4.16 (2H, d, J 13.4 Hz, *OCH*₂Ph), 4.13 (1H, dd, J 29.4, 11.7 Hz, *PhCH*), 2.42-2.31 (1H, m, *CHCH*₂*CH*), 2.21-2.11 (1H, m, *CHCH*₂*CH*); δ_C (75.5 MHz; MeOH); 144.2, 140.3, 134.2, 129.7, 129.4, 129.0, 128.9, 128.5, 84.1, 71.9, 46.3; δ_B (160.5 MHz; MeOH); 3.71; δ_F (377 MHz; MeOH); -144.01; HRMS (ESI) *calcd* C₁₇H₁₇BF₃O for [M]⁻ m/z 305.1325 found m/z 305.1330

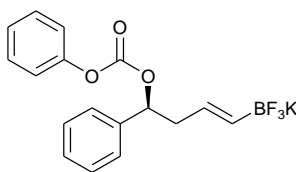
5.8.4 Potassium (*S,E*)-benzoic acid 1-phenyl-but-3-enyl ester trifluoroborate (2.195)



Using the general procedure (*S,E*)-benzoic acid 1-phenyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-but-3-enyl ester (**2.187**) (1.3 g, 3.44 mmol) was reacted with potassium hydrogen difluoride (2.35 g, 30.21 mmol) to afford the title compound as a white solid (1.06 g, 86% yield).

Mp; decomposes at 198 °C; $[\alpha]_D^{20} = +4$ ($c=1.00$, MeOH); ν_{\max} (neat)/ cm^{-1} : 2159, 2028, 1977 (C-H), 1724 (C=O), 1644 (C=C), 1270, 1231 (ester C-O), 1124, 1085 (ether C-O), 1026, 1001, 948 (B-F); δ_{H} (300 MHz; MeOH): 7.88 (1H, dd, J 8.4, 1.3 Hz, Ar), 7.43 (1H, tt, J 7.7, 1.3 Hz, Ar), 7.3-7.31 (2H, m, Ar), 7.29-7.24 (2H, m, Ar), 7.20-7.01 (4H, m, Ar), 5.77 (1H, dd, J 7.8, 5.7 Hz, PhCH), 5.62 (1H, dt, J 17.6, 6.5 Hz, CHCHB), 5.40 (1H, ddd, J 17.6, 3.9, 1.1 Hz, CHCH₂CH), 2.64-2.53 (1H, m, CHCH₂CH), 2.51-2.40 (1H, m, CHCH₂CH); δ_{C} (75.5 MHz; MeOH): 168.1, 142.7, 134.7, 132.9, 132.2, 131.0, 130.0, 129.9, 129.6, 129.2, 127.9, 127.5, 79.0, 44.6; δ_{B} (160.5 MHz; MeOH): 3.69; δ_{F} (377 MHz; MeOH) -142.83; HRMS (ESI) *calcd* for C₁₇H₁₅BF₃O₂ [M]⁻ m/z 319.1123 found m/z 319.1115

5.8.5 Potassium (*S,E*)-carbonic acid phenyl ester 1-phenyl-but-3-enyl ester trifluoroborate (2.196)

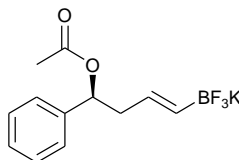


Under the standard conditions (*S,E*)-carbonic acid phenyl ester 1-phenyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-but-3-enyl ester (**2.196**) (1.87 g, 4.75 mmol) was reacted with potassium hydrogen difluoride (2.34 g, 30 mmol) to afford the title compound as a white solid (1.2 g, 68% yield).

$[\alpha]_D^{20} = -3$ ($c=1.00$, MeOH); ν_{\max} (neat)/ cm^{-1} : 2161, 2034, 1976 (C-H), 1641 (C=C), 1169, 1109, 977 (B-F); δ_{H} (400 MHz; MeOH): 7.39-7.15 (10H, m, Ar), 5.8 (1H, dt, J 18.0, 6.8 Hz, CHCHB), 5.52 (1H, dq, J 18.0, 3.9 Hz, CHCH₂CH), 4.64 (1H, t, J 6.7 Hz,

PhCHCH₂), 2.46-2.42 (2H, m, CHCH₂CH); δ_C (75.5 MHz; MeOH); 144.9, 133.0, 128.0, 126.7, 125.8, 74.1, 45.7, 23.5; δ_B (160.5 MHz; MeOH); -3.04; δ_F (377 MHz; MeOH); -142.53; HRMS (ESI⁺) *calcd* for C₁₇H₁₅BF₃O₃ [M]⁺ *m/z* 335.1072 found *m/z* 335.1020

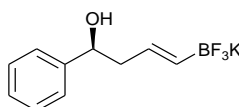
5.8.6 Potassium (*S,E*)-acetic acid 1-phenyl but-3-enyl ester trifluoroborate (2.197)



Under the standard conditions (*S,E*)-acetic acid 1-phenyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-but-3-enyl ester (**2.189**) (1.2 g, 3.8 mmol) was reacted with potassium hydrogen difluoride (2.66 g, 34.16 mmol) to afford the title compound as a white solid (0.76 g, 68% yield).

Mp; 60-62 °C; $[\alpha]_D^{20} = -31$ (*c*=1.00, MeOH); ν_{\max} (neat)/cm⁻¹; 2983 (C-H), 1718 (C=O), 1647 (C=C), 1288, 1245 (C-O), 1089, 1020, 939 (B-F); δ_H (300 MHz; MeOH); 7.34-7.32 (5H, m, Ar), 5.83-5.65 (1H, m, CHCHB), 5.71 (1H, dd, *J* 8.1, 5.7 Hz, PhCH), 5.56-5.44 (1H, m, CHCHB), 2.78-2.39 (2H, m CHCH₂CH), 2.05 (3H, s, CH₃); δ_C (75.5 MHz; MeOH); 173.1, 142.7, 132.9, 129.8, 129.2, 128.0, 127.6, 78.2, 44.5, 25.4; δ_B (160.5 MHz; MeOH); 3.63; δ_F (377 MHz; MeOH); -142.86; HRMS (ESI⁺) *calcd* for C₁₂H₁₃BF₃O₂ [M]⁺ *m/z* 257.0961 found *m/z* 257.0943

5.8.7 Potassium (*S,E*)-(4-hydroxy-4-phenylbut-1-en-1-yl) trifluoroborate (2.198)

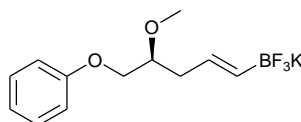


Under the standard conditions 2-[(*E*)-(*S*)-4-(*tert*-butyl-dimethyl-silanyloxy)-4-phenyl-but-1-enyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**2.190**) (1.74 g, 4.48 mmol) was reacted with potassium hydrogen difluoride (3.14 g, 40.3 mmol) to afford the title compound as a white solid (0.264 g, 23% yield).

Mp; decomposes at 236 °C; $[\alpha]_D^{20} = -5.2$ (*c*=0.77, MeOH); ν_{\max} (neat)/cm⁻¹; 2982 (C-H), 1640 (C=C), 1166, 1059, 1017 (B-F); δ_H (300 MHz; DMSO); 7.29 (4H, d, *J* 4.3 Hz, ArH), 7.19 (1H, sextet, *J* 4.4 Hz, ArH), 5.44 (1H, dt, *J* 17.4, 6.3 Hz, CHCHB), 5.25

(1H, dq, J 17.7, 3.5 Hz, CHCHB), 4.43 (1H, dd, J 10.5, 6.7 Hz, ArCH), 2.32-2.15 (2H, m, CHCH₂); δ_C (75.5 MHz; DMSO); 146.5, 130.4, 130.3, 127.8, 126.4, 126.0, 79.2, 73.3, 46.4; δ_B (96 MHz; DMSO); 3.49 HRMS (ESI⁺) *calcd* for C₁₀H₁₁BF₃O [M]⁺ m/z 254.0492 found m/z 215.0438

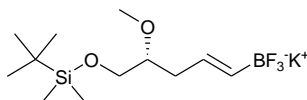
5.8.8 Potassium (*S,E*)-2-(4-Methoxy-4-phenoxy-but-1-enyl) trifluoroborate (2.199)



Under the general procedure (*S,E*)-2-(4-methoxy-4-phenoxy-but-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**2.191**) (3.15 g, 9.9 mmol) was reacted with potassium hydrogen difluoride (6.9 g, 89 mmol) to afford the title compound as a white solid (2.1 g, 71% yield).

Mp; 136-138 °C; $[\alpha]_D^{20} = +13$ ($c=1.00$, MeOH); ν_{\max} (neat)/cm⁻¹; 2923, 2841 (C-H); 1648 (C=C); 1495, 1450 (aromatic C-H); 1247 (aromatic C-O); 1173 (C-O); 1123 (C-O); 1100, 1081, 997 (B-F); δ_H (300 MHz; MeOH); 7.20-7.15 (2H, m, Ar), 6.86 (3H, m, Ar), 5.76 (1H, dt, J 17.8, 6.5 Hz, CHCHB), 5.50-5.40 (1H, m, CHCHB), 3.99 (1H, dd, J 10.3, 3.2 Hz, PhOCHH), 3.85 (1H, dd, J 10.3, 6.3 Hz, PhOCHH), 3.57-3.49 (1H, m, CH₂CHCH₂), 2.38-2.18 (2H, m, CHCH₂CHCH); δ_C (75.5 MHz; MeOH); 160.8, 133.1, 130.9, 122.2, 116.1, 81.8, 71.0, 38.7; δ_B (160.5 MHz; MeOH); 3.69; δ_F (377 MHz; MeOH); -142.87; HRMS (ESI⁺) *calcd* for C₁₂H₁₆BF₃⁺ [M]⁺ m/z 259.1123 found m/z 259.1116

5.8.9 Potassium (*R,E*)-(5-((*tert*-butyldimethylsilyl)oxy)-4-methoxypent-1-en-1-yl) trifluoroborate (2.200)

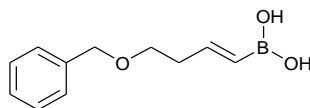


Following the general procedure (*R,E*)-2-[5-(*tert*-butyl-dimethyl-silanyloxy)-4-methoxy-pent-1-enyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**2.192**) (0.43 g, 1.20 mmol) was reacted with potassium hydrogen difluoride (6.9 g, 89 mmol) to afford the title compound as a white solid (0.10 g, 25% yield).

$[\alpha]_D^{20} = +1$ ($c=1.00$, MeOH); ν_{\max} (neat)/ cm^{-1} ; 2978 (C-H), 1632 (C=C), 1169 (C-O), 1106 (O-Si); δ_{H} (500 MHz; MeOH); 6.65 (1H, dt, J 18.0, 6.9 Hz, CHCHB), 5.49 (1H, dt, J 18.0, 1.3 Hz, CHCHB), 4.01 (1H, dd, J 10.1, 4.2 Hz, OCHH), 3.96 (1H, dd, J 10.2, 5.5 Hz, OCHH), 3.68 (1H, quintet, J 5.7 Hz, CH_2CHCH_2), 3.46 (3H, s, OCH_3), 2.56-.47 (2H, m, CH_2CHCH), 1.32 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 1.1 (6H, s, $\text{Si}(\text{CH}_3)_2$; δ_{C} (75.5 MHz; MeOH); 151.0, 84.5, 70.2, 57.9, 38.7, 30.9, 25.1, 2.0; δ_{B} (160.5 MHz; MeOH); 0.30; δ_{F} (377 MHz; MeOH); -142.27

5.9 Potassium alkenyl trifluoroborate hydrolysis

5.9.1 (*E*)-(4-(benzyloxy)but-1-en-1-yl)boronic acid (2.202)

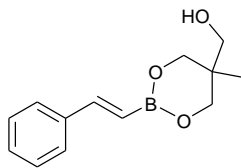


To a solution of potassium (*E*)-(4-(benzyloxy)but-1-en-1-yl)trifluoroborate (**2.140**) (1.0 g, 3.73 mmol) in acetonitrile/ H_2O (2:1, 35 mL), was added lithium hydroxide (0.313 g, 13.05 mmol). The reaction was stirred at room temperature for 20 h then acidified with a saturated solution of NH_4Cl (20 mL) and 1M HCl (6 mL). The mixture was extracted with ethyl acetate (3 x 25 mL) and combined organic washings dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford the title compound as a colourless oil (0.65 g, 85 % yield).

ν_{\max} (neat)/ cm^{-1} ; 3030, 2976 (aryl C-H) 2852, 2795 (alkyl C-H), 1635 (C=C), 1496, 1453 (aryl C=C), 1358, 1328 (B-O), 1113, 1097 (C-O); δ_{H} (300 MHz; CDCl_3); 7.35-7.27 (5H, m, ArH), 5.62 (1H, dt, J 17.7, 1.4 Hz, CHCHB), 5.53 (1H, dt, J 18.0, 1.5 Hz, CHCHB), 4.54 (2H, s, ArCH_2O), 3.60 (2H, t, J 6.7 Hz, OCH_2CH_2), 2.59-2.52 (2H, m, CH_2CHCH); δ_{C} (75.5 MHz; CDCl_3); 153.8, 138.4, 128.5, 127.8, 127.7, 73.0, 68.9, 36.0; δ_{B} (96 MHz; CDCl_3); 32.11

5.10 Synthesis of (*E*)-alkenyl dioxaborinanes

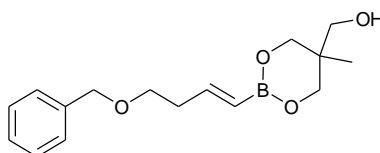
5.10.1 (5-Methyl-2-styryl-[1,3,2]dioxaborinan-5-yl)-methanol (2.203)



(*E*)-Styrylboronic acid (1.50 g, 10.14 mmol) was dissolved in toluene (20 mL) and 1,1,1-tris(hydroxymethyl)ethane (1.22 g, 10.14 mmol) added. Water was removed by azeotropic distillation by the Dean-Stark method overnight. The reaction was concentrated *in vacuo* to afford the crude boronate (2.35 g, 99% yield).

δ_{H} (300 MHz; CDCl_3); 7.49-7.47 (2H, *ArH*), 7.36-7.27 (4H, m, *ArH*, *CHCHB*), 6.08 (1H, d, *J* 18.3 Hz (*CHCHB*)), 4.02-3.70 (6H, br.s, $\text{C}(\text{CH}_2)_3$), 1.70 (1H, br.s, OH), 0.96 (3H, s, CCH_3); δ_{C} (75.5 MHz; CDCl_3); 147.5, 137.7, 128.7, 128.6, 127.1, 68.0, 36.9, 17.4 (C-B not observed); δ_{B} (96 MHz; CDCl_3); 29.19

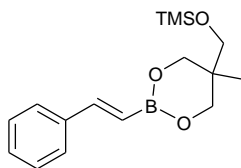
5.10.2 [2-(4-Benzyloxy-but-1-enyl)-5-methyl-[1,3,2]dioxaborinan-5-yl]-methanol (2.204)



To a solution of toluene (20 mL) and (*E*)-(4-(benzyloxy)but-1-en-1-yl)boronic acid (2.202) (0.50 g, 2.40 mmol) was added 1,1,1-tris(hydroxymethyl)ethane (0.292 g, 2.40 mmol). Water was removed by azeotropic distillation by the Dean-Stark method overnight. The reaction was concentrated *in vacuo* to afford the crude boronate (0.69 g, 99% yield).

δ_{H} (300 MHz; CDCl_3); 7.34-7.31 (5H, m, *ArH*), 6.54 (1H, dt, *J* 17.8, 6.5 Hz, *CHCHB*), 5.42 (1H, dt, *J* 17.8, 1.5 Hz, *CHCHB*), 4.5 (2H, s, ArCH_2O), 3.70 (6H, br.s $\text{C}(\text{CH}_2)_3$), 3.55 (2H, t, *J* 6.9 Hz, OCH_2CH_2), 2.52-2.43 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}$), 1.72 (1H, br.s, OH), 0.92 (3H, s, CCH_3); δ_{C} (75.5 MHz; CDCl_3); 150.5, 138.5, 128.4, 127.8, 127.6, 83.2, 73.0, 69.2, 69.9, 36.8, 35.9, 17.4 (C-B not observed); δ_{B} (96 MHz; CDCl_3); 28.85

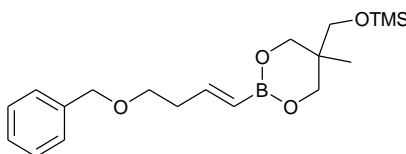
5.10.3 5-Methyl-2-styryl-5-trimethylsilanyloxymethyl-[1,3,2]dioxaborinane (2.205)



In anhydrous THF (20 mL) was dissolved (5-methyl-2-styryl-[1,3,2]dioxaborinan-5-yl)-methanol (**2.203**) (2.35 g, 10.14 mmol) and the solution cooled to 0 °C. Triethylamine (4.24 mL, 30.42 mmol) was added and the reaction stirred for 30 min. Trimethylsilyl chloride (1.93 mL, 15.21 mmol) was added slowly and the reaction warmed to room temperature overnight. Water (10 mL) was then added and the mixture extracted with ethyl acetate (3 x 20 mL). Combined organic washings were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified through a short silica plug (eluting with ethyl acetate) to afford the title compound as a white solid (3.08 g, 99% yield).

Mp; 54-56 °C; ν_{max} (neat)/cm⁻¹; 3025, 2956, 2902 (C-H), 1625 (C=C), 1344, 1330, 1311 (B-O), 1066 (O-Si); δ_{H} (300 MHz; CDCl₃); 7.50-7.47 (2H, m, ArH), 7.36-7.26 (4H, m, ArH, CHCHB), 6.09 (1H, d, *J* 18.3 Hz, CHCHB), 3.95 (2H, d, *J* 11.0 Hz, OCH₂), 3.70 (2H, d, *J* 11.0 Hz, OCH₂), 3.48 (2H, s, CH₂OSi(CH₃)₃), 0.92 (3H, s, CCH₃), 0.11 (9H, s, Si(CH₃)₃); δ_{C} (75.5 MHz; CDCl₃); 147.2, 137.9, 128.6, 127.1, 68.1, 64.6, 36.9, 17.8, -0.6; δ_{B} (96 MHz; CDCl₃); 28.64

5.10.4 2-(4-Benzyloxy-but-1-enyl)-5-methyl-5-trimethylsilanyloxymethyl-[1,3,2]dioxaborinane (2.206)



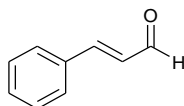
In anhydrous THF (10 mL) was dissolved [2-(4-benzyloxy-but-1-enyl)-5-methyl-[1,3,2]dioxaborinan-5-yl]-methanol (**2.204**) (0.69 g, 2.38 mmol) and the solution cooled to 0 °C. Triethylamine (1.25 mL, 9.0 mmol) was added and the reaction stirred for 30 min. Trimethylsilyl chloride (0.57 mL, 4.50 mmol) was added slowly and the reaction warmed to room temperature overnight. Water (10 mL) was then added and the mixture extracted with ethyl acetate (3 x 20 mL). Combined organic washings were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude

product was purified through a short silica plug (eluting with: ethyl acetate) to afford the title compound as a white oil (0.84 g, 99% yield).

ν_{\max} (neat)/ cm^{-1} ; 2941, 2919, 2873 (C-H), 1640 (C=C), 1395, 1376, 1363 (B-O), 1005 (Si-O); δ_{H} (300 MHz; CDCl_3); 7.33-7.28 (5H, m, ArH), 6.52 (1H, dt, J 17.8, 6.5 Hz, CH_2CHCHB), 5.41 (1H, dt, J 17.8, 1.3 Hz, CHCHB), 4.50 (2H, s, ArCH_2O), 3.87 (2H, d, J 11.9 Hz, OCHHCCHHO), 3.73 (2H, d, J 11.9 Hz, OCHHCCHHO), 3.68 (2H, s, CCH_2OSi), 3.55 (2H, t, J 6.7 Hz, OCH_2CH_2), 2.51-2.35 (2H, m, CH_2CHCH), 0.91 (3H, s, CCH_3), 0.07 (9H, s, $\text{SiC}(\text{CH}_3)_3$); δ_{C} (75.5 MHz; CDCl_3); 150.4, 138.3, 128.3, 127.7, 127.5, 72.8, 69.1, 68.8, 66.6, 36.7, 35.8, 17.3, 0.97 (C-B not observed); δ_{B} (96 MHz; CDCl_3); 28.96

5.11 Preparation of compounds for gas chromatography study

5.11.1 3-Phenyl-propenal (3.41)

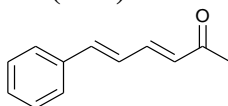


Pyridinium chlorochromate (6.40 g, 29.8 mmol) was dissolved (as a slurry) in dichloromethane (40 mL). A solution of cinnamylalcohol (**3.40**) (1.92 mL, 14.90 mmol) in dichloromethane (10 mL) was added. The flask was stoppered and the solution stirred at room temperature for 3 h while protected from light. The reaction mixture was diluted with diethyl ether (20 mL), filtered through Fluorosil and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a pale yellow oil (0.802 g, 51% yield).

R_{f} (petrol/ethyl acetate, 4:1); 0.59; ν_{\max} (neat)/ cm^{-1} ; 2981 (C-H), 1674 (C=O), 1626 (C=C), 1597, 1577, 1496 (C=C aryl); δ_{H} (300 MHz; CDCl_3); 9.71 (1H, d, J 7.7 Hz, COH), 7.59-7.55 (2H, m, ArH), 7.48 (1H, d, J 16.0 Hz, ArCHCH), 7.45-7.41 (3H, m, ArH), 6.72 (1H, dd, J 16.0, 7.7 Hz, ArCHCH); δ_{C} (75.5 MHz; CDCl_3); 193.8, 152.9, 134.0, 131.3, 129.2, 128.6, 128.5

All data in accordance with literature values ¹⁷

5.11.2 6-Phenyl-hexa-3,5-dien-2-one (3.37)

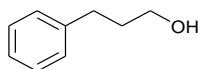


A solution of 3-phenyl-propenal (**3.41**) (0.80 g, 6.05 mmol) and 1-(triphenylphosphanylidene)-propan-2-one (**3.45**) (1.68 g, 5.26 mmol) in chloroform (30 mL) was heated under reflux for 4 h. The mixture was cooled to room temperature and the solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 8:2) to afford the title compound as a yellow oil (0.52 g, 50% yield).

R_f (petrol/ethyl acetate, 4:1); 0.42; ν_{\max} (neat)/ cm^{-1} ; 3061, 3029, 2981 (C-H), 1700 (C=O), 1635, 1627 (C=C), 1599, 1575, 1495 (C=C aryl); δ_H (300 MHz; CDCl_3); 7.50-7.46 (2H, m, ArH), 7.40-7.34 (3H, m, ArH), 7.33-7.29 (1H, m, CHCHCO), 6.99 (1H, d, J 15.5 Hz, ArCH), 6.88 (1H, dd, J 15.6, 15.6 Hz, ArCHCHCH), 6.26 (1H, d, J 15.5 Hz, CHCO), 2.32 (3H, s, COCH_3); δ_C (75.5 MHz; CDCl_3); 198.6, 143.5, 141.3, 136.0, 130.6, 129.3, 128.9, 127.3, 126.7, 27.5; HRMS (ESI^+) *calcd* for $\text{C}_{12}\text{H}_{13}\text{O}_1$ $[\text{M}+\text{H}]^+$ m/z 173.0966 found m/z . 173.0968

All data in accordance with literature values¹⁸

5.11.3 3-Phenyl-propan-1-ol (3.42)

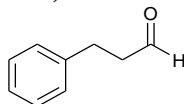


Cinnamylalcohol (3.0 g, 22 mmol) was dissolved in anhydrous ethanol (50 mL) under an inert atmosphere and palladium on carbon added (0.30 g, 10% wt.). The reaction was then subjected to an atmosphere of $\text{H}_{2(g)}$ and stirred at room temperature overnight. The reaction was filtered through celite (eluting with diethyl ether) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 6:4) to afford the title compound as a colourless oil (2.06 g, 69% yield).

R_f (petrol/ethyl acetate, 4:1); 0.48; ν_{\max} (neat)/ cm^{-1} ; 3366 (O-H), 3059, 3027, 2934, 2902 (C-H), 1603, 1496 (C=C aryl); δ_H (300 MHz; CDCl_3); 7.33-7.27 (2H, m, ArH), 7.21-7.16 (3H, m, ArH), 3.68 (2H, t, J 6.4 Hz, CH_2OH), 2.72 (2H, t, J 7.4 Hz, ArCH_2), 1.95-1.86 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.54 (1H, br.s, OH); δ_C (75.5 MHz; CDCl_3); 141.9, 128.5, 128.4, 126.0, 62.4, 34.3, 34.2

All data in accordance with literature values¹⁹

5.11.4 3-Phenyl-propionaldehyde (3.43)

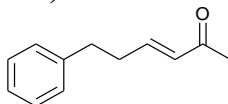


Pyridinium chlorochromate (6.3 g, 29.4 mmol) was dissolved (as a slurry) in dichloromethane (40 mL). A solution of 3-phenyl-propan-1-ol (**3.42**) (2.0 g, 14.90 mmol) in dichloromethane (10 mL) was added. The flask was stoppered and the solution stirred at room temperature for 3 h while protected from light. The reaction mixture was diluted with diethyl ether (20 mL), filtered through Fluorosil and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (1.23 g, 62% yield).

R_f (petrol/ethyl acetate, 4:1); 0.64; δ_H (300 MHz; $CDCl_3$); 9.83 (1H, t, J 1.4 Hz, COH), 7.33-7.27 (2H, m, ArH), 7.23-7.19 (3H, m, ArH), 2.97 (2H, t, J 7.6 Hz, ArCH₂), 2.81-2.76 (2H, m, CH₂CO); δ_C (75.5 MHz; $CDCl_3$); 201.6, 140.4, 128.7, 128.4, 126.4, 45.4, 28.2

All data in accordance with literature values²⁰

5.11.5 6-Phenyl-hex-3-en-2-one (3.36)

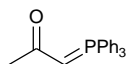


A solution of 3-phenyl-propionaldehyde (**3.43**) (1.2 g, 8.94 mmol) and 1-(triphenylphosphanylidene)-propan-2-one (**3.45**) (2.48 g, 7.78 mmol) in chloroform (50 mL) was heated under reflux for 4 h. The mixture was cooled to room temperature and the solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a pale yellow oil (0.92 g, 68% yield).

R_f (petrol/ethyl acetate, 4:1); 0.50; ν_{max} (neat)/cm⁻¹; 3028, 2981, 2928 (C-H), 1697 (C=O), 1672 (C=C), 1626, 1603, 1497 (C=C); δ_H (300 MHz; $CDCl_3$); 7.33-7.28 (2H, m, ArH), 7.23-7.17 (3H, m, ArH), 6.82 (1H, dt, J 15.9, 6.8 Hz, CH₂CH), 6.10 (1H, d, J 15.9 Hz, CHCHCO), 2.80 (2H, t, J 8.1 Hz, ArCH₂), 2.56 (2H, q, J 7.0 Hz, CH₂CH), 2.23 (3H, s, COCH₃); δ_C (75.5 MHz; $CDCl_3$); 198.7, 147.1, 140.7, 131.8, 128.6, 128.4, 126.3, 34.5, 34.2, 27.0; HRMS (ESI^+) *calcd* for C₁₂H₁₄NaO₁ [M+Na]⁺ m/z 197.0942 found: m/z . 197.0942

All data in accordance with literature values²¹

5.11.6 1-(Triphenyl-phosphanylidene)-propan-2-one (3.45)

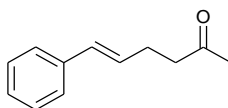


A solution of triphenylphosphine (6.80 g, 25.9 mmol) and chloroacetone (1.72 mL, 21.62 mmol) in dichloromethane (20 mL) was refluxed with stirring for 18 h. The reaction was concentrated to half volume *in vacuo* and the remaining solution poured into ice cold diethyl ether (75 mL). The resulting solid is filtered off and washed with cold diethyl ether (2 x 25 mL) to afford the salt. The salt is added to a solution of Na₂CO₃ (2.52 g, 23.78 mmol) in water (25 mL) and stirred at room temperature for 24 h. The white precipitate is filtered off and washed with water until the effluent is neutral. The resulting powder is air dried by suction to afford the title compound as a white powder (6.45 g, 78% yield).

ν_{\max} (neat)/cm⁻¹; 3048, 2991 (C-H), 1534, 1479, 1435, 1384; δ_{H} (300 MHz; CDCl₃); 7.69-7.61 (6H, m, ArH), 7.57-7.50 (3H, m, ArH), 7.47-.41 (6H, m, ArH), 3.69 (1H, d, *J* 25.0 Hz, COCH), 2.09 (3H, d, *J* 1.74 Hz, CH₃CO); δ_{C} (75.5 MHz; CDCl₃); 190.9, 133.1, 132.0, 128.8, 127.9, 126.7, 52.5, 28.5; δ_{P} (122 MHz; CDCl₃); 15.5; HRMS (*ESI*⁺) *calcd* for C₂₁H₁₉NaOP [M+Na]⁺ *m/z* 341.1071 found: *m/z* 341.170.

All data in accordance with literature values²²

5.11.7 6-Phenyl-hex-5-en-2-one (3.34)

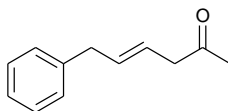


An oven dried, 24 mL screw-capped vial equipped with a rubber septum was charged with potassium (*E*)-styryl trifluoroborate salt (**2.117**) (0.30 g, 1.43 mmol), [Rh(OH)(cod)]₂ (0.0098 g, 0.021 mmol), cyclooctadiene (0.0043 g, 0.043 mmol) and potassium hydroxide (0.016 g, 0.285 mmol). The reaction vessel was purged with argon and dioxane (2 mL) and water (0.2 mL) were subsequently added by syringe. The red solution was stirred for 15 minutes at room temperature, before the addition of methyl vinyl ketone (0.05 g, 0.71 mmol). The reaction was transferred to a preheated hotplate at 80 °C for 20 h. Upon completion, the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution: diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column

chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as pale yellow oil (0.94 g, 77% yield).

R_f (petrol/ethyl acetate, 4:1); 0.42; ν_{\max} (neat)/ cm^{-1} ; 3063, 3030, 2982 (C-H), 1709 (C=O), 1603, 1584, 1495 (C=C aryl); δ_H (300 MHz; CDCl_3); 7.35-7.28 (4H, m, ArH), 7.22 (1H, m, ArH), 6.40 (1H, dt, J 15.8, 1.2 Hz, ArCH), 6.19 (1H, dt, J 15.8, 6.7 Hz, ArCHCH), 2.62 (2H, t, J 6.7 Hz, COCH_2), 2.52-2.44 (2H, m, COCH_2CH_2), 2.17 (3H, s, CH_3); δ_C (75.5 MHz; CDCl_3); 208.2, 137.5, 130.8, 128.9, 128.6, 127.2, 126.1, 43.3, 30.1, 27.2; HRMS (ESI⁺) *calcd* for $\text{C}_{12}\text{H}_{15}\text{O}$ $[\text{M}+\text{H}]^+$ m/z 175.1123 found: m/z 175.1119 All data in accordance with literature values¹¹

5.11.8 6-Phenyl-hex-4-en-2-one (3.35)

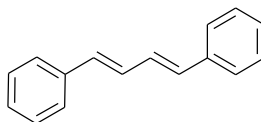


An oven dried, 24 mL screw-capped vial equipped with a rubber septum was charged with potassium (*E*)-styryl trifluoroborate salt (**2.117**) (0.30 g, 1.43 mmol), $[\text{Rh}(\text{C}_2\text{H}_4)\text{Cl}]_2$ (0.0028 g, 0.007 mmol), dppf (0.016 g, 0.029 mmol) and lithium hydroxide (0.085 g, 3.57 mmol). The reaction vessel was purged with argon and dioxane (2.34 mL) and water (1.76 mL) were subsequently added by syringe. The red solution was stirred for 15 minutes at room temperature, before the addition of methyl vinyl ketone (0.05g, 0.71 mmol). The reaction was transferred to a preheated hotplate at 80 °C for 20 h. Upon completion, the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution: diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as pale yellow oil (0.11 g, 89% yield).

R_f (petrol/ethyl acetate, 4:1); 0.58; ν_{\max} (neat)/ cm^{-1} ; 3062, 3028, 2981 (C-H), 1701 (C=O), 1602, 1584, 1495 (C=C aryl); δ_H (300 MHz; CDCl_3); 7.33-7.28 (2H, m, ArH), 7.23-7.17 (3H, m, ArH), 5.87-5.68 (2H, m, CHCH), 3.41 (2H, d, J 7.0 Hz, ArCH_2), 3.30 (2H, d, J 6.8 Hz, CH_2CO), 2.12 (3H, s, CH_3); δ_C (75.5 MHz; CDCl_3); 206.6, 140.1, 131.9, 128.6, 128.3, 126.2, 122.0, 42.4, 33.7, 29.7

All data in accordance with literature values²³

5.11.9 (*E,E*)-1,4-diphenyl-1,3-butadiene (3.38)

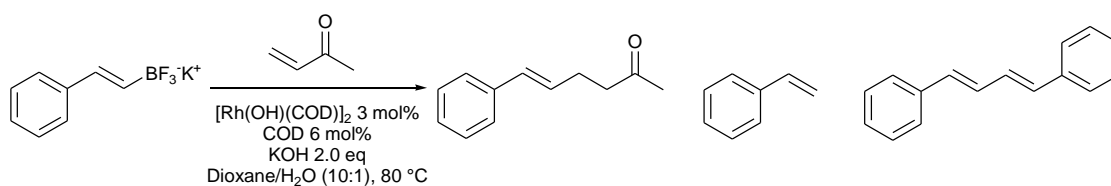


Isolated as a by-product during the rhodium catalysed conjugate addition of potassium (*E*)-styryl trifluoroborate salt (**2.117**) to methylvinyl ketone as described in 5.11.7.

Mp; 150 °C; (Lit²⁴ 150-152 °C) ν_{\max} (neat)/cm⁻¹; 3056, 3016, 2999, 2934 (C-H), 1688, 1609 (C=C), 1594, 1572, 1489 (C=C aryl); δ_{H} (300 MHz; CDCl₃); 7.46-7.43 (4H, m, ArH), 7.33 (4H, t, *J* 7.5 Hz, ArH), 6.96 (2H, dd *J* 11.9, 2.8 Hz, ArCH), 6.68 (2H, dd, *J* 11.9, 2.8 Hz, ArCHCH); δ_{C} (75.5 MHz; CDCl₃); 137.5, 132.9, 129.3, 128.7, 127.7, 126.5

All data in accordance with literature values²⁴

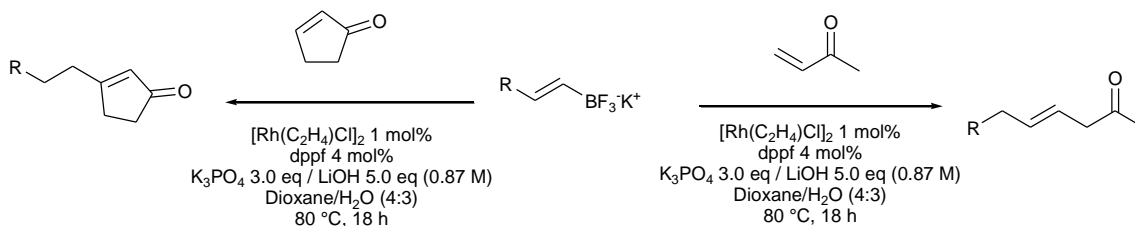
5.12 General procedure for the rhodium catalysed conjugate addition reaction followed by gas chromatography



An oven dried, 24 mL screw-capped vial equipped with a rubber septum was charged with potassium *trans*-styryl trifluoroborate salt (**2.117**) (0.060 g, 0.285 mmol), [Rh(OH)(cod)]₂ (0.002g, 0.0043 mmol), cyclooctadiene (0.087 g, 0.0858 mmol), KOH (0.016 g, 0.285 mmol) and the standard dihexylether (0.034 mL, 0.143 mmol). The reaction vessel was purged with argon and dioxane (1 mL) and water (0.1 mL) were subsequently added by syringe. The red solution was stirred for 15 minutes at room temperature, before the addition of methyl vinyl ketone (0.012 mL, 0.143 mmol). The reaction was transferred to a preheated hotplate at 80 °C at time = 0 min. Over the course of the reaction aliquots (0.025 mL) were taken *via* syringe. They were immediately diluted to 1 mL in dioxane and filtered through a syringe filter to remove the catalyst. Each aliquot was then analysed by gas chromatography recording the peak area for each component over time.

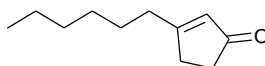
5.13 Rhodium catalysed olefin transposition reactions

5.13.1 General procedure for rhodium catalysed olefin transposition



An oven dried, 24 mL screw-capped vial equipped with a rubber septum was charged with alkenylpotassium trifluoroborate salt (0.204 g, 1.019 mmol), [Rh(C₂H₄)₂Cl]₂ (0.002g, 0.005 mmol), dppf (0.011 g, 0.020 mmol) and lithium hydroxide (0.061 g, 2.5 mmol). The reaction vessel was purged with argon and dioxane (1.6 mL) and water (1.2 mL) were subsequently added by syringe. The red solution was stirred for 15 minutes at room temperature, before the addition of enone (0.044 mL, 0.51 mmol). The reaction was transferred to a preheated hotplate at 80 °C for 20 h. Upon completion, the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution; diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel to give the desired products.

5.13.2 3-Hexyl-cyclopent-2-enone (3.52)

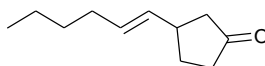


Potassium (*E*)-hex-1-enyl trifluoroborate (**2.113**) (0.232 g, 1.22 mmol) was reacted with cyclopentenone (0.05 g, 0.61 mmol) under olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (0.055 g, 55% yield).

R_f (petrol/ethyl acetate, 4:1); 0.32; ν_{max} (neat)/cm⁻¹; 2981, 2972, 2929 (C-H), 1705, 1674 (C=O), 1615 (C=C); δ_H (300 MHz; CDCl₃); 5.88 (1H, quintet, *J* 1.5 Hz *CH*CO), 2.52-2.49 (2H, m *COCH*₂), 2.36-2.28 (4H, m, *CH*₂*CCH*₂), 1.23-1.17 (8H, m, *CH*₃(*CH*₂)₄*CH*₂), 0.79 (3H, t, *J* 6.3 Hz, *CH*₂*CH*₃); δ_C (75.5 MHz; CDCl₃); 210.3, 183.4, 129.4, 35.3, 33.5, 31.5, 30.0, 27.02, 22.5, 14.0; HRMS (*ESI*⁺) calcd for C₁₁H₁₉O [M+H]⁺ *m/z* 167.1436 found *m/z* 167.1434

All data in accordance with literature values²⁵

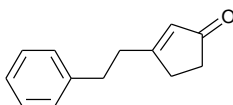
5.13.3 3-Hex-1-enyl-cyclopentanone (3.53)



During olefin transposition optimisation reacting potassium (*E*)-hex-1-enyl trifluoroborate (**2.113**) with cyclopentenone, the title compound was isolated as the minor product as a yellow oil.

R_f (petrol/ethyl acetate, 4:1); 0.40; ν_{\max} (neat)/ cm^{-1} ; 2959, 2928 (C-H), 1741 (C=O), 1699 (C=C); δ_H (300 MHz; CDCl_3); 5.54-5.38 (2H, m, CHCH), 2.83-2.72 (1H, m, COCH_2CH), 2.41-2.23 (2H, m, COCH_2CH_2), 2.21-2.08 (2H, m, COCH_2CH), 2.04-1.94 (2H, m, $(\text{CH}_2)\text{CH}_2\text{CH}$), 1.76-1.61 (2H, m, $\text{CHCH}_2\text{CH}_2\text{O}$), 1.38-1.23 (4H, m, $\text{CH}_3(\text{CH}_2)_2$), 0.89 (3H, t, J 6.3 Hz, CH_3); δ_C (75.5 MHz; CDCl_3); 219.5, 132.0, 130.7, 45.1, 39.9, 38.3, 32.2, 31.6, 30.0, 22.3, 14.0

5.13.4 3-Phenethyl-cyclopent-2-enone (3.54)

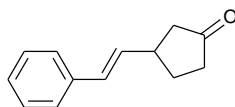


Potassium *trans*-styryltrifluoroborate (**2.117**) (0.126 g, 0.6 mmol) was reacted with cyclopentenone (0.025 mL, 0.3 mmol) under olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (0.048 g, 86% yield).

R_f (petrol/ethyl acetate, 4:1); 0.55; ν_{\max} (neat)/ cm^{-1} ; 3027, 2923 (C-H), 1702 (C=O), 1672 (C=C), 1614 (C=C aryl); δ_H (300 MHz; CDCl_3); 7.33-7.27 (2H, m, ArH), 7.24-7.17 (3H, m, ArH), 5.98 (1H, quintet, J 1.4, CHCO), 2.91 (2H, t, J 8.2 Hz, ArCH_2), 2.71 (2H, t, J 7.9 Hz, COCH_2), 2.61-2.57 (2H, m, ArCH_2CH_2), 2.41-2.38 (2H, m, COCH_2CH_2); δ_C (75.5 MHz; CDCl_3); 210.0, 181.8, 140.6, 129.9, 128.7, 128.2, 126.4, 35.4, 35.1, 33.4, 31.8; HRMS (ESI^+) *calcd* for $\text{C}_{13}\text{H}_{14}\text{NaO}$ [$\text{M}+\text{Na}$] $^+$ m/z 209.0942 found m/z 209.0950

All data in accordance with literature values²⁶

5.13.5 3-Styryl-cyclopentanone (3.55)

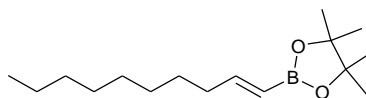


3-Styryl-cyclopentanone was isolated as a yellow oil as the minor product during optimisation of the rhodium catalysed olefin transposition reaction of potassium *trans*-styryl trifluoroborate (**2.113**) with cyclopentenone.

R_f (petrol/ethyl acetate, 4:1); 0.40; ν_{\max} (neat)/ cm^{-1} ; 3092, 2961, 2869 (C-H), 1716 (C=O), 1616 (C=C), 1526 (C=C aryl); δ_H (300 MHz; CDCl_3); 7.38-7.29 (4H, m, ArH), 7.25-7.20 (1H, m, ArH), 6.46 (1H, d, J 15.8 Hz, ArCHCH), 6.22 (1H, dd, J 15.8 Hz, ArCHCH), 3.09-2.96 (1H, m, COCH_2CH), 2.49 (1H, dd, J 18.3, 7.6 Hz, COCHHCH), 2.43-2.22 (3H, m, CHHCOCH_2), 2.14 (1H, ddd, J 18.1, 10.4, 1.1 Hz, CHCHHCH_2), 1.89-1.77 (1H, m, CHCHHCH_2); δ_C (75.5 MHz; CDCl_3); 218.6, 137.1, 132.1, 129.9, 128.7, 127.5, 126.2, 44.9, 40.3, 38.3, 30.0; HRMS (ESI^+) *calcd* for $\text{C}_{13}\text{H}_{14}\text{NaO}$ [$M+H^+$] m/z 209.0942 found: m/z 209.0930

All data in accordance with literature values ²⁷

5.13.6 2-Dec-1-enyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane



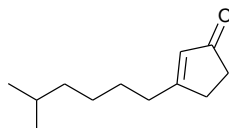
Decyne (0.65 mL, 3.60 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.52 mL, 3.6 mmol) were charged to a 25 mL Schlenk tube under a positive pressure of dry argon. To the resulting solution was added bis(cyclopentadienyl)zirconium(IV) chloride hydride (0.093 g, 0.36 mmol) followed by triethylamine (0.05 mL, 0.36 mmol). The mixture was capped and then heated at 60 °C for 16 hours with protection from light. Upon completion, hexane (5 mL) was added and the mixture stirred for 10 minutes in air. The material was isolated through a short silica pad (elution: hexanes) and concentrated under reduced pressure to afford the title compound as a pale yellow oil (0.909 g, 95% yield).

ν_{\max} (neat)/ cm^{-1} ; 2980, 2925, 2855 (C-H), 1638 (C=C), 1318, 1361 (B-O), 1145 (C-B); δ_H (300 MHz; CDCl_3); 6.62 (1H, dt, J 17.9, 6.4 Hz, CHCHB), 5.41 (1H, dt, J 17.9, 1.4 Hz, CHCHB), 2.17-2.10 (2H, m, CH_2CH), 1.42-1.38 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}$), 1.26 (22H,

br.s, $\text{CH}_3(\text{CH}_2)_5$, $(\text{CH}_3)_2\text{CC}(\text{CH}_3)_2$, 0.87 (3H, t, J 7.0 Hz, $\text{CH}_3(\text{CH}_2)_5$); δ_{C} (75.5 MHz; CDCl_3); 155.0, 83.0, 35.9, 32.0, 29.5, 29.3, 28.3, 24.8, 22.8, 14.2 (C-B not observed); δ_{B} (96 MHz; CDCl_3); 29.01; HRMS (ESI^+) *calcd* for $\text{C}_{16}\text{H}_{32}\text{BO}_2$ $[\text{M}+\text{H}]^+$ m/z 267.2495 found m/z 267.2478

All data in accordance with literature values²⁸

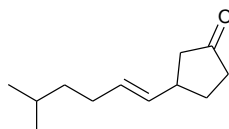
5.13.7 3-(5-Methyl-hexyl)-cyclopent-2-enone (3.60)



Potassium (*E*)-5-methyl-hex-1-enyl-trifluoroborate (**2.116**) (0.249 g, 1.22 mmol) was reacted with cyclopentenone (0.050 g, 0.609 mmol) under the olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethylacetate 9:1) to afford the title compound as a colourless oil (0.085 g, 78% yield).

R_f (petrol/ethyl acetate, 4:1); 0.29; ν_{max} (neat)/ cm^{-1} ; 2957, 2933, 2862 (C-H), 1703 (C=O), 1614 (C=C); δ_{H} (300 MHz; CDCl_3); 5.94 (1H, m, CHCO), 2.60-2.55 (2H, m, COCH_2), 2.45-2.36 (4H, m, CH_2CCH_2), 1.60-1.50 (3H, m, $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{CH}_2$), 1.39-1.30 (2H, m, $\text{CCH}_2\text{CH}_2\text{CH}_2$), 1.20 (2H, dd, J 9.1, 6.6 Hz, $(\text{CH}_3)_2\text{CHCH}_2$), 0.87 (6H, d, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$); δ_{C} (75.5 MHz; CDCl_3); 209.3, 182.4, 128.5, 37.8, 34.4, 32.7, 30.7, 27.0, 26.5, 26.2, 21.7; HRMS (ESI^+) *calcd* for $\text{C}_{11}\text{H}_{18}\text{O}_3$ $[\text{M}+\text{H}]^+$ m/z 167.143 found m/z 167.144

5.13.8 3-(5-Methyl-hex-1-enyl)-cyclopentanone (3.61)

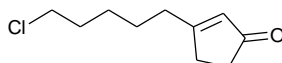


During optimisation of rhodium catalysed olefin transposition of potassium (*E*)-5-methyl-hex-1-enyl-trifluoroborate (**2.116**) with cyclopentenone the title compound was isolated as the minor isomer as a yellow oil.

R_f (petrol/ethyl acetate, 4:1); 0.55; ν_{max} (neat)/ cm^{-1} ; 2955, 2928, 2870 (C-H), 1742 (C=O); δ_{H} (300 MHz; CDCl_3); 5.53-5.38 (2H, m, CHCH), 2.85-2.72 (1H, m,

CH₂CHCH₂), 2.43-2.23 (2H, m, COCH₂CH), 2.21-2.08 (2H, m, COCH₂CH₂), 2.03-1.93 (2H, m, CH₂CHCH), 1.75-1.61 (2H, m, COCH₂CH₂), 1.58-1.47 (1H, m, CH(CH₃)₂), 1.33-1.17 (4H, m, (CH₂)₂CH(CH₃)₂), 0.87 (6H, d, *J* 6.6 Hz, C(CH₃)₂); δ_C (75.5 MHz; CDCl₃); 219.5, 131.8, 130.9, 45.1, 39.9, 38.7, 38.3, 30.4, 30.1, 27.6, 22.6; HRMS (*ESI*⁺) *calcd* for C₁₂H₂₀NaO [M+Na]⁺ *m/z* 203.1412 found *m/z* 203.1393

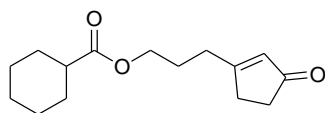
5.13.9 3-(5-Chloro-pentyl)-cyclopent-2-enone (3.62)



Potassium (*E*)-5-chloro-pent-1-enyltrifluoroborate (**2.115**) (0.222 g, 1.218 mmol) was reacted with cyclopentenone (0.050 g, 0.609 mmol) under the olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 4:1) to afford the title compound as a yellow oil (0.034 g, 27% yield).

R_f (petrol/ethyl acetate, 4:1); 0.13; ν_{max} (neat)/cm⁻¹; 2937, 2864 (C-H), 1703 (C=O), 1615 (C=C), 733 (C-Cl); δ_H (300 MHz; CDCl₃); 5.97-5.94 (1H, m, CCHCO), 3.55 (2H, t, *J* 6.6 Hz, ClCH₂), 2.62-2.55 (2H, m, COCH₂CH₂), 2.44-2.37 (4H, m, CH₂CCH₂), 1.82 (2H, quintet, *J* 6.9 Hz, ClCH₂CH₂CH₂), 1.69-1.57 (2H, m, CH₂CH₂CH₂C), 1.56-1.45 (2H, m, CH₂CH₂CH₂C); δ_C (75.5 MHz; CDCl₃); 210.0, 182.4, 129.6, 44.8, 35.3, 33.4, 32.3, 31.6, 26.6, 26.4; HRMS (*ESI*⁺) *calcd* for C₁₀H₁₅ClO [M+H]⁺ *m/z* 187.088 found *m/z* 187.089

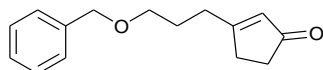
5.13.10 Cyclohexanecarboxylic acid 3-(3-oxo-cyclopent-1-enyl)-propyl ester (3.64)



Potassium (*E*)-(3-((cyclohexanecarbonyl)oxy)prop-1-en-1-yl)trifluoroborate (**2.121**) (0.334 g, 1.22 mmol) was reacted with cyclopentenone (0.050 g, 0.609 mmol) under olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 4:1) to afford the title compound as a colourless oil (0.041 g, 27%).

R_f (petrol/ethyl acetate, 4:1); 0.36; ν_{\max} (neat)/ cm^{-1} ; 2930, 2867 (C-H), 1706, 1674 (C=O), 1612 (C=C), 1172 (C-O); δ_H (300 MHz; CDCl_3); 5.88 (1H, quintet, J 1.41 Hz, COCH), 2.52-2.49 (2H, m, OCH_2), 2.34 (4H, m, $\text{COCH}_2\text{CCH}_2$), 1.49-1.43 (6H, m), 1.09-1.01 (10H, m); δ_C (75.5 MHz; CDCl_3); 183.75, 129.83, 60.79, 41.74, 36.47, 35.71, 31.93, 27.74, 23.05

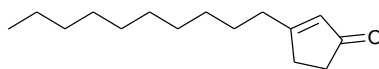
5.13.11 Cyclohexanecarboxylic acid 3-(3-oxo-cyclopent-1-enyl)-propyl ester (3.65)



Potassium (*E*)-(3-(benzyloxy)prop-1-en-1-yl)trifluoroborate (**2.120**) (0.334 g, 1.22 mmol) was reacted with cyclopentenone (0.050 g, 0.609 mmol) under olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethylacetate 4:1) to afford the title compound as a colourless oil (0.041 g, 27%).

ν_{\max} (neat)/ cm^{-1} ; 2986 (C-H), 1704 (C=O), 1665 (C=C), 1618, 1604, 1512 (C=C aryl), 1254, 1188 (C-O); δ_H (300 MHz; CDCl_3); 5.88 (1H, quintet, J 1.41 Hz, COCH), 2.52-2.49 (2H, m, OCH_2), 2.37-2.31 (4H, m, $\text{COCH}_2\text{CCH}_2$), 1.49-1.43 (6H, m), 1.09-1.01 (10H, m); δ_C (75.5 MHz; CDCl_3); 183.8, 129.8, 60.8, 41.7, 36.5, 35.7, 31.9, 27.7, 23.1; HRMS (ESI^+) calcd for $\text{C}_{15}\text{H}_{18}\text{O}_2$ $[\text{M}+\text{H}]^+$ m/z 253.1205 found m/z 253.1204
All data in accordance with literature values²⁵

5.13.12 3-Decyl-cyclopent-2-enone (3.57)

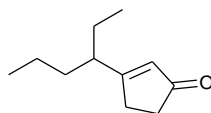


Potassium (*E*)-decenyl trifluoroborate (**2.114**) (0.30 g, 1.22 mmol) was reacted with cyclopentenone (0.05 g, 0.61 mmol) under olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (0.125 g, 92% yield).

R_f (petrol/ethyl acetate, 4:1); 0.38; δ_H (300 MHz; CDCl_3), 5.87 (1H, m, CHCO), 2.52-2.49 (2H, m, COCH), 2.37-2.31 (4H, m, CH_2CCH_2), 1.50 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{C}$), 1.20 (12H, t, J 3.5 Hz, $\text{CH}_3\text{CH}_2(\text{CH}_2)_6$), 1.11-1.01 (2H, m, CH_3CH_2), 0.78 (3H, t, J 6.3 Hz,

CH_3CH_2); δ_{C} (75.5 MHz; CDCl_3); 210.5, 183.6, 129.9, 41.8, 36.5, 32.3, 30.0, 29.9, 29.8, 29.7, 29.5, 28.1, 27.5, 23.1, 14.5; HRMS (ESI^+) calcd for $\text{C}_{14}\text{H}_{26}\text{O}$ $[\text{M}+\text{H}]^+$ m/z 223.205 found m/z 223.206

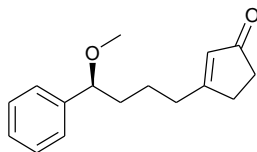
5.13.13 3-(1-Ethyl-butyl)-cyclopent-2-enone (3.66)



Potassium (*E*)-1-ethyl-but-1-enyl-trifluoroborate (**2.122**) (0.349 g, 1.22 mmol) was reacted with cyclopentenone (0.050 g, 0.61 mmol) under the general olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (0.039 g, 39% yield).

R_f (petrol/ethyl acetate, 4:1); 0.52; ν_{max} (neat)/ cm^{-1} ; 2981, 2972, 2932, 2890 (C-H), 1708, 1673 (C=O), 1607 (C=C); δ_{H} (300 MHz; CDCl_3); 5.86 (1H, q, J 1.68 Hz, CHCO), 2.54-2.50 (2H, m, COCH_2); 2.47-2.45 (1H, m, CH_2CHCH_2), 2.33 (2H, t, J 4.74 Hz, COCH_2CH_2), 1.48-1.39 (2H, m, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}$), 1.22-1.16 (4H, m, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CHCH}_2\text{CH}_3$), 0.80 (6H, t, J 6.55 Hz, CH_3CH_2); δ_{C} (75.5 MHz; CDCl_3); 210.6, 188.2, 129.9, 37.9, 35.5, 29.8, 29.4, 23.1, 19.3, 14.4, 11.8; HRMS (ESI^+) calcd for $\text{C}_{11}\text{H}_{18}\text{ONa}$ $[\text{M}+\text{Na}]^+$ m/z 189.130 found m/z 189.124

5.13.14 (*S*)-3-(4-methoxy-4-phenylbutyl)cyclopent-2-enone (3.68)

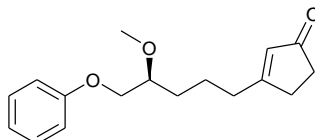


Potassium (*S,E*)-4-methoxy-4-phenylbut-1-enyl trifluoroborate (**2.193**) (0.327 g, 1.22 mmol) was reacted with cyclopentenone (0.050 g, 0.61 mmol) under the general olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 8:2) to afford the title compound as a colourless oil (0.030 g, 20% yield).

R_f (petrol/ethyl acetate, 4:1); 0.05; $[\alpha]_D^{20} = -43$ ($c=0.3$, CHCl_3); ν_{max} (neat)/ cm^{-1} ; 2933, 2823 (C-H), 1705 (C=O), 1673 (C=C), 1610 (C=C aryl), 1100 (C-O); δ_{H} (300 MHz;

CDCl₃); 7.31-7.25 (5H, m, ArH), 5.92-5.90 (1H, m, CHCO), 4.13-4.09 (1H, m, ArCH), 3.21 (3H, s, OCH₃), 2.54-2.50 (2H, m, COCH₂), 2.41-2.36 (2H, m, CH₂CCH₂), 1.74-1.52 (4H, m, ArCHCH₂CH₂); δ_C (75.5 MHz; CDCl₃); 210.2, 182.7, 142.0, 136.6, 129.7, 128.6, 127.8, 126.7, 83.7, 56.8, 37.8, 35.4, 33.4, 31.5, 23.4; HRMS (*ESI*⁺) *calcd* for C₁₆H₂₀NaO₂ [M+Na]⁺ *m/z* 267.1361 found *m/z* 267.1342

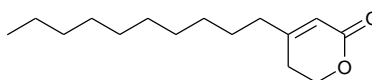
5.13.15 (*S*)-3-(4-methoxy-5-phenoxy-pentyl)cyclopent-2-enone (3.69)



Potassium (*S,E*)-2-(4-Methoxy-4-phenoxy-but-1-enyl) trifluoroborate (**2.199**) (0.182 g, 0.61 mmol) was reacted with cyclopentenone (0.025 g, 0.30 mmol) under the general olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 7:3) to afford the title compound as a colourless oil (0.028 g, 34% yield).

R_f (petrol/ethyl acetate, 4:1); 0.09; [α]_D²⁰ = -20 (*c*=1.00, CHCl₃); δ_H (300 MHz; CDCl₃); 7.23-7.21 (2H, m, ArH), 6.93-6.83 (3H, m, ArH), 5.92 (1H, s, CHCO), 3.95 (1H, dd, *J* 9.8, 5.1 Hz, OCHHCH), 3.89 (1H, dd, *J* 9.8, 4.8 Hz, OCHHCH), 3.54-3.47 (1H, m, CHOCH₃), 3.42 (3H, s, OCH₃), 2.54-2.52 (2H, m, COCH₂), 2.43-2.38 (2H, m, CH₂CH₂CH₂), 2.37-2.33 (2H, m, COCH₂CH₂), 1.78-1.71 (2H, m, CH₂CH₂CH₂C), 1.69-1.58 (2H, m, OCHCH₂CH₂); δ_C (75.5 MHz; CDCl₃); 210.2, 182.6, 158.7, 129.7, 129.5, 121.0, 114.5, 79.1, 69.2, 58.0, 35.4, 33.6, 31.5, 22.9; HRMS (*ESI*⁺) *calcd* for C₁₇H₂₂O₃Na [M+Na]⁺ *m/z* 297.1467 found *m/z* 297.1538

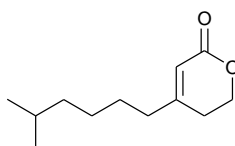
5.13.16 4-Decyl-5,6-dihydro-pyran-2-one (3.70)



Potassium (*E*)-decenyl trifluoroborate (**2.114**) (0.100 g, 0.4 mmol) was reacted with 5,6-dihydropyran-2-one (0.020 g, 0.20 mmol) under the general conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (0.017 g, 36% yield).

R_f (petrol/ethyl acetate, 4:1); 0.40; ν_{\max} (neat)/ cm^{-1} ; 2980, 2957, 2934, 2854 (C-H), 1704 (C=O); δ_H (300 MHz; CDCl_3); 5.80 (1H, t, J 1.4 Hz, CHCO), 4.37 (2H, t, J 6.2 Hz, OCH_2CH_2), 2.37 (2H, t, J 6.0 Hz, OCH_2CH_2), 2.25 (2H, t, J 7.6 Hz, $(\text{CH}_2)_8\text{CH}_2\text{C}$), 1.54 (6H, br.s, $\text{CCH}_2(\text{CH}_2)_3$), 1.27 (10H, br.s, $(\text{CH}_2)_3(\text{CH}_2)_5\text{CH}_3$), 0.88 (3H, t, J 6.5 Hz, CH_3); δ_C (75.5 MHz; CDCl_3); 178.1, 161.8, 115.8, 66.1, 36.7, 32.0, 29.6, 29.6, 29.4, 29.3, 29.2, 28.0, 26.5, 22.8, 14.2; HRMS (ESI^+) *calcd* for $\text{C}_{15}\text{H}_{27}\text{O}_2$ $[\text{M}+\text{H}]^+$ m/z 239.2011 found m/z 239.1549

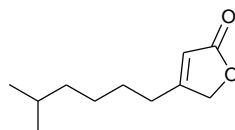
5.13.17 4-(5-Methyl-hexylidene)-tetrahydro-pyran-2-one (3.71)



Potassium (*E*)-5-methyl-hex-1-enyl-borane (**2.116**) (0.208 g, 1.019 mmol) was reacted with 5,6-dihydropyran-2-one (0.050 g, 0.5097 mmol) under olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (0.080 g, 80% yield).

R_f (petrol/ethyl acetate, 4:1); 0.24; ν_{\max} (neat)/ cm^{-1} ; 2955, 2870 (C-H), 1743 (C=O), 1254, 1219 (C-O); δ_H (300 MHz; CDCl_3); 5.79 (1H, quintet, J 1.3 Hz, CCHCH_2), 4.36 (2H, t, J 6.2 Hz, OCH_2), 2.36 (2H, t, J 6.6 Hz, CCH_2), 2.25 (2H, t, J 7.4 Hz, OCH_2CH_2), 2.01 (1H, m, $(\text{CH}_3)_2\text{CH}$), 1.57-1.44 (2H, m, $\text{CH}_2\text{CH}_2\text{C}$), 1.36-1.34 (4H, m, $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2$), 0.87 (6H, d, J 6.8 Hz, $(\text{CH}_3)_2\text{CH}$); δ_C (75.5 MHz; CDCl_3); 178.1, 161.8, 115.8, 66.1, 32.0, 38.5, 28.6, 27.8, 27.5, 26.9, 22.5; HRMS (ESI^+) *calcd* for $\text{C}_{12}\text{H}_{20}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ m/z 219.1361 found m/z 219.1351

5.13.18 4-(6-Methyl-heptyl)-5H-furan-2-one (3.72)

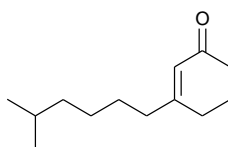


Potassium (*E*)-5-methyl-hex-1-enyl-trifluoroborate (**2.116**) (0.170 g, 0.833 mmol) was reacted with 5H-furan-2-one (0.030 g, 0.417 mmol) under the general olefin transposition conditions. Crude product was purified by flash column chromatography

on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (0.010 g, 13% yield).

R_f (petrol/ethyl acetate, 4:1); 0.38; ν_{\max} (neat)/ cm^{-1} ; 2981, 2971, 2931, 2869 (C-H), 1779 (C=O), 1747 (C=C); δ_H (300 MHz; CDCl_3); 5.86-5.82 (1H, m, CHCO), 4.74 (2H, d, J 1.7 Hz, OCH_2), 2.41 (2H, t, J 7.5 Hz, CHCCH_2), 1.48-1.63 (3H, m, $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{CH}_2$), 1.30-1.41 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2$), 1.26-1.13 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.87 (6H, d, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$); δ_C (75.5 MHz; CDCl_3) 174.2, 170.6, 115.4, 73.0, 38.5, 28.6, 27.8, 27.5, 26.9, 22.5; HRMS (ESI^+) calcd for $\text{C}_{11}\text{H}_{18}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ m/z 205.1204 found m/z 205.1191

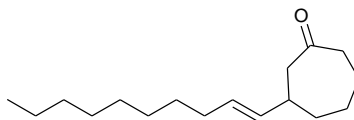
5.13.19 3-(5-Methyl-hexyl)-cyclohex-2-enone (3.73)



Potassium (*E*)-5-methyl-hex-1-enyl-trifluoroborate (**2.116**) (0.149 g, 0.728 mmol) was reacted with cyclohexenone (0.035 g, 0.364 mmol) under the general conditions. Crude product was purified using flash column chromatography on silica gel (eluting with petrol/ethyl acetate 4:1) to afford the title compound as a yellow oil (0.035 g, 49% yield).

R_f (petrol/ethyl acetate, 4:1); 0.43; ν_{\max} (neat)/ cm^{-1} ; 2981, 2972, 2890 (C-H), 1667 broad (C=O), 1625 (C=C); δ_H (300 MHz; CDCl_3); 5.80-5.86 (1H, m, CHCO), 2.35 (2H, t, J 6.7 Hz, COCH_2), 2.28 (2H, t, J 5.9 Hz, $\text{COCH}_2\text{CH}_2\text{CH}_2$), 2.21 (2H, t, J 7.6 Hz, COCHCCH_2), 1.98 (2H, COCH_2CH_2), 1.57-1.42 (3H, m, $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{CH}_2$), 1.36-1.24 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2$), 1.23-1.13 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.86 (6H, d, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$); δ_C (75.5 MHz; CDCl_3); 200.0, 166.7, 125.6, 38.7, 38.1, 37.4, 29.7, 27.9, 27.2, 27.0, 22.8, 22.6; HRMS (ESI^+) calcd for $\text{C}_{13}\text{H}_{23}\text{O}$ $[\text{M}+\text{H}]^+$ m/z 195.1749 found m/z 195.1734

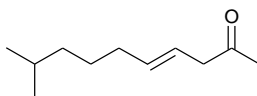
5.13.20 3-Dec-1-enyl-cycloheptanone (3.75)



Potassium (*E*)-decenyl trifluoroborate (**2.114**) (0.156 g, 0.635 mmol) was reacted with cycloheptenone (0.035 g, 0.32 mmol) under the general olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (0.033 g, 41% yield).

R_f (petrol/ethyl acetate, 4:1); 0.78; ν_{\max} (neat)/ cm^{-1} ; 2923, 2854 (C-H), 1670 (C=O); δ_H (300 MHz; CDCl_3); 5.56-5.26 (2H, m, CHCH), 2.52-2.42 (4H, m, CH_2COCH_2), 1.96-1.87 (3H, m, CH_2CHCHCH), 1.63-1.36 (4H, m, $\text{COCH}_2\text{CH}_2\text{CH}_2$), 1.25 (14H, br.s, $(\text{CH}_2)_6\text{CHCHCHCH}_2$), 0.87 (3H, t, CH_3); δ_C (75.5 MHz; CDCl_3); 214.5, 134.2, 129.3, 50.0, 44.1, 39.1, 37.5, 32.5, 32.0, 29.5, 29.4, 29.2, 28.5, 24.1, 22.7, 14.2; HRMS (ESI^+) calcd for $\text{C}_{17}\text{H}_{31}\text{O}$ $[\text{M}+\text{H}]^+$ m/z 251.2375 found m/z 251.2362

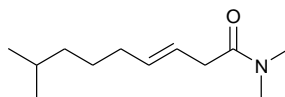
5.13.21 9-Methyl-dec-4-en-2-one (3.76)



Potassium (*E*)-5-methyl-hex-1-enyl-trifluoroborate (**2.116**) (0.291 g, 1.426 mmol) was reacted with methyl vinyl ketone (0.050 g, 0.713 mmol) under olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 19:1) to afford the title compound as a colourless oil (0.081 g, 68% yield).

R_f (petrol/ethyl acetate, 4:1); 0.78; ν_{\max} (neat)/ cm^{-1} ; 2955, 2929, 2870 (C-H), 1716 (C=O), 1677 (C=C); δ_H (300 MHz; CDCl_3); 5.54-5.45 (2H, m, CHCH); 3.11 (2H, dd, J 6.9, 5.8 Hz, CHCH_2CO), 2.12 (3H, d, J 3.8 Hz, COCH_3), 1.99-1.93 (2H, m, $\text{CH}_2\text{CH}_2\text{CHCH}$), 1.48 (6H, nonet, J 6.6 Hz, $(\text{CH}_3)_2\text{CHCH}_2$), 1.39-1.28 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 1.16-1.13 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.83 (6H, d, J 6.63 Hz, $(\text{CH}_3)_2\text{CH}$); δ_C (75.5 MHz; CDCl_3); 207.9, 135.8, 122.1, 48.1, 38.9, 33.2, 28.2, 27.3, 22.9, 21.4; HRMS (ESI^+) calcd for $\text{C}_{11}\text{H}_{21}\text{O}$ $[\text{M}+\text{H}]^+$ m/z 169.1592 found m/z 169.1594

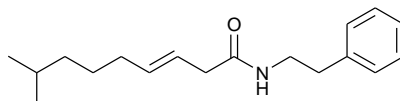
5.13.22 8-Methyl-non-3-enoic acid dimethylamide (3.77)



Potassium (*E*)-5-methyl-hex-1-enyl-trifluoroborate (**2.116**) (0.124 g, 0.605 mmol) was reacted with dimethylacrylamide (0.03 g, 0.303 mmol) under the general conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 7:3) to afford the title compound as a pale yellow oil (0.054 g, 90% yield).

R_f (petrol/ethyl acetate, 4:1); 0.09; ν_{\max} (neat)/ cm^{-1} ; 2981, 2972, 2931(C-H), 1643 (broad) (C=O) (C=C); δ_H (300 MHz; CDCl_3); 5.62-5.48 (2H, m, CHCH), 3.10 (2H, d, 4.3 Hz, COCH_2CH), 2.97 (6H, s, $(\text{CH}_3)_2\text{N}$), 2.03 (2H, app. dd, J 12.5, 7.1 Hz, CH_2CHCH), 1.50 (1H, septet, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$), 1.30-1.42 (2H, m, $\text{CH}_2\text{CH}_2\text{CHCH}$), 1.12-1.22 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.86 (6H, d, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$); δ_C (75.5 MHz; CDCl_3); 171.6, 132.7, 121.9, 38.6, 37.3, 35.5 32.7, 27.9, 27.8, 27.1, 22.6; HRMS (ESI^+) calcd for $\text{C}_{12}\text{H}_{23}\text{NO}$ $[\text{M}+\text{H}]^+$ m/z 198.1858 found m/z 198.1856

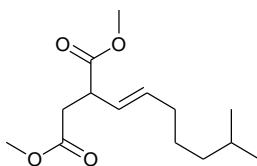
5.13.23 8-Methyl-non-3-enoic acid phenethyl-amide (3.78)



Potassium (*E*)-5-methyl-hex-1-enyl-trifluoroborate (**2.116**) (0.116 g, 0.571 mmol) was reacted with *N*-phenylethylacrylamide (0.05 g, 0.286 mmol) under the general conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 8:2) to afford the title compound as a pale yellow oil (0.060 g, 76% yield).

ν_{\max} (neat)/ cm^{-1} ; 3184 (N-H), 2981, 2974, 2902 (C-H), 1660 (C=O), 1644 (C=C); δ_H (300 MHz; CDCl_3); 7.31-7.17 (3H, m, Ar), 7.17-7.08 (2H, m, Ar), 5.66 (1H, br.s, NH), 5.61-5.51 (1H, m, COCH_2CH), 5.48-5.33 (1H, m, COCH_2CHCH), 3.44 (2H, q, J 6.7 Hz, $\text{CH}_2\text{CH}_2\text{Ar}$), 2.91 (2H, d, J 7.5 Hz, CHCH_2CO), 2.75 (2H, q, J 6.7 Hz, $\text{CH}_2\text{CH}_2\text{Ar}$), 1.89 (2H, app.q, J 7.3 Hz, $\text{CH}_2\text{CH}_2\text{CH}$), 1.45 (1H, septet, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$), 1.31-1.18 (2H, m, CHCH_2CH_2), 1.14-1.03 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.80 (6H, d, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$); δ_C (75.5 MHz; CDCl_3); 170.1, 138.7, 135.5, 128.7, 128.6, 126.5, 121.5, 40.6, 38.5, 35.6, 35.2, 27.8, 27.4, 27.0, 22.5; HRMS (ESI^+) calcd for $\text{C}_{18}\text{H}_{28}\text{NO}$ $[\text{M}+\text{H}]^+$ m/z 274.21709 found m/z 274.2177

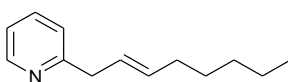
5.13.24 8-Methyl-2-(2-oxo-propyl)-non-3-enoic acid methyl ester (3.79)



Potassium (*E*)-5-methyl-hex-1-enyl-trifluoroborate (**2.116**) (0.129 g, 0.63 mmol) was reacted with dimethylitaconate (0.050 g, 0.316 mmol) using the general conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (0.028 g, 37% yield).

R_f (petrol/ethyl acetate, 4:1); 0.67; ν_{\max} (neat)/ cm^{-1} ; 2981, 2971 (C-H), 1736 broad (C=O) (C=C); δ_H (300 MHz; CDCl_3); 5.57 (1H, dtd, J 10.6, 7.4, 0.7 Hz, COCHCHCH), 5.27 (1H, dtd, J 10.6, 9.8, 1.6 Hz, COCHCHCH), 3.80 (1H, ddd, J 9.7, 5.9, 0.8 Hz, CH_2CHCO), 3.69 (3H, s, OCH_3), 3.67 (3H, s, COCH_3), 2.84 (1H, dd, J 16.6, 8.7 Hz, CHHCH), 2.44 (1H, dd, J 16.6, 8.7 Hz, CHHCH), 2.16-2.02 (2H, m, CHCH_2CH_2), 1.52 (1H, septet, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$), 1.42-1.29 (2H, m, CHCH_2CH_2), 1.23-1.12 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.86 (6H, d, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$); δ_C (75.5 MHz; CDCl_3); 173.7, 172.0, 134.5, 124.9, 52.1, 51.8, 40.0, 38.5, 36.5, 27.8, 27.7, 27.1, 22.6; HRMS (ESI^+) *calcd* for $\text{C}_{14}\text{H}_{25}\text{O}_4$ $[\text{M}+\text{H}]^+$ m/z 257.1747 found m/z 257.1729

5.13.25 2-Oct-2-enyl-pyridine (3.80)

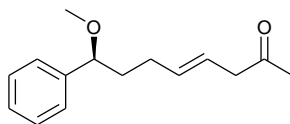


Potassium (*E*)-hex-1-enyl trifluoroborate (**2.113**) (0.181 g, 0.95 mmol) was reacted with vinylpyridine (0.05 g, 0.48 mmol) under the general conditions. Crude product was purified by flash column chromatography (eluting with petrol/ethyl acetate 95:5) to afford the title compound as a colourless oil (0.036 g, 46% yield).

R_f (petrol/ethyl acetate, 4:1); 0.57; ν_{\max} (neat)/ cm^{-1} ; 2956, 2927, 2857 (C-H), 1693 (C=C), 1670 (C=N aryl), 1620, 1588, 1568 (C=C aryl); δ_H (300 MHz; CDCl_3); 8.53 (1H, d, J 3.6 Hz, NCH), 7.59 (1H, td, J 7.7, 1.8 Hz, NCCHCH), 7.16 (1H, d, J 7.8 Hz, NCCH), 7.10 (1H, dd, J 7.1, 5.3 Hz, NCHCH), 5.72-5.54 (2H, m, CHCH), 3.60 (2H, d, J 6.7 Hz, ArCH_2CH), 2.15 (2H, q, J 7.1 Hz, $\text{CHCH}_2(\text{CH}_2)_3$), 1.42-1.35 (2H, m,

$\text{CH}_2(\text{CH}_2)_2\text{CH}_3$), 1.32-1.28 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.88 (3H, t, J 6.9 Hz, CH_3); δ_{C} (75.5 MHz; CDCl_3); 161.2, 149.3, 136.5, 132.3, 126.1, 122.6, 121.1, 36.4, 31.6, 29.3, 27.4, 22.6, 14.1; HRMS (ESI^+) calcd for $\text{C}_{13}\text{H}_{20}\text{N}$ $[\text{M}+\text{H}]^+$ m/z 190.1596 found m/z 190.1619

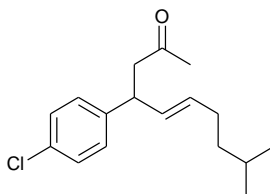
5.13.26 8-Methoxy-8-phenyl-oct-4-en-2-one (3.81)



Potassium (*S,E*)-4-methoxy-4-phenylbut-1-enyl trifluoroborate (**2.193**) (0.191 g, 0.71 mmol) was reacted with methylvinylketone (0.025 g, 0.357 mmol) under the general olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 8:2) to afford the title compound as a yellow oil (0.069 g, 83% yield).

R_f (petrol/ethyl acetate, 4:1); 0.41; $[\alpha]_D^{20} = -25$ ($c=1.3$, CHCl_3); ν_{max} (neat)/ cm^{-1} ; 2981, 2890 (C-H), 1711 (C=O), 1677 (C=C), 1599, 1582 (C=C arene); δ_{H} (300 MHz; CDCl_3); 7.36-7.31 (2H, m, Ar), 7.31-7.24 (3H, m, Ar), 5.58 (2H, ddd, J 7.4, 3.9, 1.8 Hz, CHCH), 4.08 (1H, dd, J 7.9, 5.4 Hz, ArCHCH_2), 3.19 (3H, s, CHOCH_3), 3.14 (2H, d, J 5.7 Hz, CHCH_2CO), 2.13 (3H, s, COCH_3), 1.95-1.80 (2H, m, CHCH_2CH_2), 1.73-1.61 (2H, m, CHCH_2CH_2); δ_{C} (75.5 MHz; CDCl_3); 206.8, 142.0, 132.8, 128.4, 127.6, 126.7, 121.5, 83.0, 56.6, 42.3, 37.5, 29.5, 23.8; HRMS (ESI^+) calcd for $\text{C}_{15}\text{H}_{20}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ m/z 255.1361 found m/z 255.1351

5.13.27 4-(4-Chloro-phenyl)-9-methyl-dec-5-en-2-one (3.82)

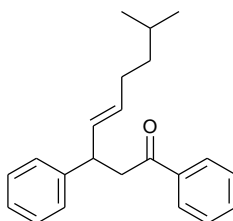


Potassium (*E*)-5-methyl-hex-1-enyl-trifluoroborate (**2.116**) (0.113 g, 0.55 mmol) was reacted with 4,4-chlorophenyl-1,3-butene-2-one (0.050 g, 0.277 mmol) using the general conditions. Crude product was purified by flash column chromatography on

silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow oil (0.054 g, 70% yield).

R_f (petrol/ethyl acetate, 4:1); 0.77; ν_{\max} (neat)/ cm^{-1} ; 2981, 2972, 2903 (C-H), 1716 (C=O), 1594 (C=C); δ_H (300 MHz; CDCl_3); 7.25 (2H, dt, J 8.4, 2.4 Hz, Ar), 7.12 (2H, dt, J 8.4, 2.4 Hz, Ar), 5.51 (1H, dd, J 15.4, 6.6 Hz, CHCHCH), 5.41 (1H, dt, J 15.4, 6.2 Hz, $\text{CH}_2\text{CH}_2\text{CH}$), 3.83 (1H, app. q, J 7.0 Hz, CHCH₂CO), 2.82 (1H, dd, J 16.2, 7.4 Hz, CHHCO), 2.75 (1H, dd, J 16.1, 7.3 Hz, CHHCO), 2.08 (3H, s, CH_3CO), 1.93-2.02 (2H, m, $\text{CH}_2\text{CH}_2\text{CHCH}$), 1.49 (1H, septet, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$), 1.20 (2H, q, J 7.8 Hz, $\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.85 (6H, d, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$); δ_C (75.5 MHz; CDCl_3); 206.9, 142.3, 132.1, 131.6, 131.5, 128.9, 128.6, 49.6, 43.1, 38.5, 30.7, 30.3, 27.5, 22.5, 22.4; HRMS (ESI^+) calcd for $\text{C}_{17}\text{H}_{23}\text{NaO}_1$ $[\text{M}+\text{Na}]^+$ m/z 301.1335 found m/z 301.1336

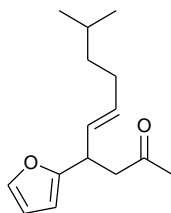
5.13.28 8-Methyl-1,3-diphenyl-non-4-en-1-one (3.83)



Potassium (*E*)-5-methyl-hex-1-enyl-trifluoroborate (**2.116**) (0.098 g, 0.48 mmol) was reacted with (0.050 g, 0.24 mmol) under the general conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow oil (0.070 g, 95% yield).

R_f (petrol/ethyl acetate, 4:1); 0.68; ν_{\max} (neat)/ cm^{-1} ; 2981, 2972 (C-H), 1723 (C=O), 1686 (C=C), 1598, 1581 (C=C aryl); δ_H (300 MHz; CDCl_3); 7.58-7.51 (1H, m, Ar), 7.48-7.40 (2H, m, Ar), 7.35-7.15 (5H, m, Ar), 5.62 (1H, dd, J 15.4, 7.1 Hz, PhCHCHCH), 5.42 (1H, dt, J 15.4, 6.6 Hz, PhCHCHCH), 4.06 (1H, app.q., J 7.2 Hz, PhCHCHCH), 3.40 (1H, dd, J 16.2, 7.8 Hz, CHHCO), 3.31 (1H, dd, J 16.1, 6.7 Hz, CHHCO), 1.96 (2H, app.dd., J 15.0, 6.9 Hz, CHCH₂CH₂), 1.47 (1H, septet, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$), 1.17 (2H, app.dd., J 15.4, 6.9 Hz, CH₂CH₂CH), 0.82 (6H, d, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$); δ_C (75.5 MHz; CDCl_3); 198.6, 144.1, 137.3, 132.9, 131.9, 131.3, 128.5, 128.4, 129.07, 127.6, 126.3, 44.8, 44.0, 38.5, 30.3, 27.5, 22.5, 22.4; HRMS (ESI^+) calcd for $\text{C}_{22}\text{H}_{27}\text{O}$ $[\text{M}+\text{H}]^+$ m/z 307.2062 found m/z 307.2053

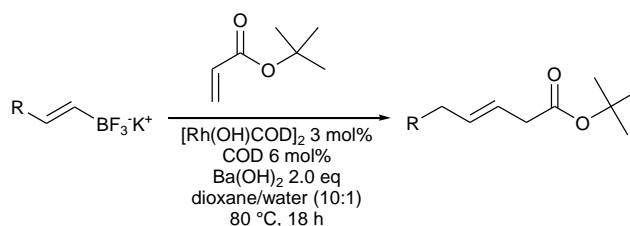
5.13.29 4-Furan-2-yl-9-methyl-dec-5-en-2-one (3.84)



Potassium (*E*)-5-methyl-hex-1-enyl-trifluoroborate (**2.116**) (0.150 g, 0.73 mmol) was reacted with *cis*-4-(2-furyl)-3-butene-2-one (0.050 g, 0.367 mmol) under the general conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow oil (0.072 g, 84% yield).

R_f (petrol/ethyl acetate, 4:1); 0.62; ν_{\max} (neat)/ cm^{-1} ; 2981, 2956, 2930 (C-H), 1717 (C=O), 1591 (C=C), 1505 (C=C); δ_H (300 MHz; CDCl_3); 7.31 (1H, dd, J 1.8, 0.8 Hz, OCHCH), 6.27 (1H, dd, J 3.1, 1.9 Hz, OCHCH), 5.99 (1H, dd, J 3.2, 0.8, OCCH), 5.49 (2H, m, $\text{CH}_2\text{CH}_2\text{CHCH}$), 3.93 (1H, q, J 6.8 Hz, CHCH_2CO), 2.89 (1H, dd, J 16.1, 6.7 Hz, CH_2CHHCH), 2.71 (1H, dd, J 16.1, 7.7 Hz, CH_2CHHCH), 2.12 (3H, s, COCH_3), 2.05-1.96 (2H, m, $\text{CH}_2\text{CH}_2\text{CHCH}$), 1.52 (1H, septet, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$), 1.24 (2H, t, J 8.7 Hz, $\text{CH}_2\text{CH}_2\text{CHCH}$), 0.86 (6H, d, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$); δ_C (75.5 MHz; CDCl_3); 206.8, 156.6, 141.3, 132.8, 128.8, 110.2, 105.0, 47.6, 38.52, 37.8, 30.5, 30.3, 27.6, 22.5, 22.5; HRMS (ESI^+) *calcd* for $\text{C}_{15}\text{H}_{23}\text{NaO}_2[\text{M}+\text{Na}]^+$ m/z 257.1518 found m/z 257.1508

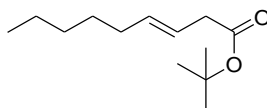
5.14 Conditions for olefin transposition to *tert*-butyl acrylate



An oven dried, 24 mL screw-capped vial equipped with a rubber septum was charged with hydroxy(cyclooctadiene)rhodium(I) dimer (0.008 g, 0.018 mmol), potassium alkenyltrifluoroborate salt (0.249 g, 1.218 mmol) and barium hydroxide octahydrate (0.209 g, 1.218 mmol). The vessel was purged with argon and 1,5-cyclooctadiene (0.0045 mL, 0.037 mmol), dioxane (2 mL) and water (0.2 mL) were added sequentially by syringe. The red solution was stirred for 15 minutes before the addition of *tert*-butyl

acrylate (0.051 mL, 0.609 mmol) in dioxane (0.5 mL). The reaction was transferred to a preheated hotplate at 80 °C for 20 h. Upon completion the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution: diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel to give the desired products.

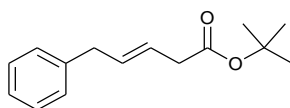
5.14.1 Non-3-enoic acid *tert*-butyl ester (3.85)



Potassium (*E*)-hex-1-enyl trifluoroborate (**2.113**) (0.148 g, 0.78 mmol) was reacted with *tert*-butyl acrylate (0.050 g, 0.39 mmol) under the standard conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow oil (0.112 g, 100%).

R_f (petrol/ethyl acetate, 4:1); 0.77; ν_{\max} (neat)/ cm^{-1} ; 2983, 2961, 2931, 2873, 2869 (C-H), 1724 (C=O), 1642 (C=C), 1151 (C-O); δ_H (300 MHz; CDCl_3); 5.40-5.49 (2H, m, *CHCH*), 2.92 (2H, d, *J* 5.7 Hz, *CHCH}_2\text{CO}*), 2.08 (2H, q, *J* 6.6 Hz, *CH}_2\text{CH}_2\text{CH}*), 1.24-1.21 (9H, m, *CH}_3(\text{CH}_2)_3*), 0.82 (9H, q, *J* 4.9 Hz, *C(CH}_3)_3*); δ_C (75.5 MHz; CDCl_3); 171.7, 134.8, 122.8, 80.7, 36.0, 33.3, 33.0, 29.4, 28.6, 22.9, 14.3; HRMS (ESI^+) *calcd* for $\text{C}_{13}\text{H}_{24}\text{O}_2$ [$M+\text{Na}$] $^+$ m/z 235.1674 found m/z 235.1656

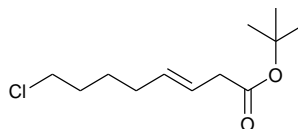
5.14.2 5-Phenyl-pent-3-enoic acid *tert*-butyl ester (3.88)



Potassium *trans*-styryl trifluoroborate (**2.117**) (0.147 g, 0.78 mmol) was reacted with *tert*-butyl acrylate (0.050 g, 0.39 mmol) under the standard conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 4:1) to afford the title compound as a colourless oil (0.054 g, 60%).

R_f (petrol/ethyl acetate, 4:1); 0.65; δ_H (300 MHz; CDCl_3), 7.49-7.44 (1H, m, Ar), 7.40-7.27 (2H, m, Ar), 7.24-7.16 (2H, m, Ar), 5.92-5.63 (2H, m, *CHCH*), 3.41 (2H, *J* 6.0 Hz, *ArCH}_2*), 3.12 (2H, d, *J* 5.7 Hz, *CH}_2\text{CO}*), 1.46 (9H, s, *C(CH}_3)_3*); δ_C (75.5 MHz; CDCl_3); 171.3, 151.4, 128.7, 128.6, 128.4, 128.3, 126.4, 83.7, 34.2, 31.2, 29.0; HRMS (ESI^+) *calcd* for $\text{C}_{15}\text{H}_{20}\text{NaO}_2$ [$M+\text{Na}$] $^+$ m/z 255.1360 found m/z 255.1351

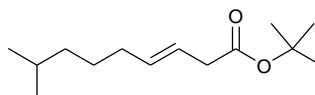
5.14.3 8-Chloro-oct-3-enoic acid *tert*-butyl ester (3.89)



Potassium (*E*)-5-chloro-pent-1-enyltrifluoroborate (**2.115**) (0.164 g, 0.78 mmol) was reacted with *tert*-butyl acrylate (0.050 g, 0.39 mmol) under the general conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 20:1) to afford the title compound as a yellow oil (0.077 g, 85%).

R_f (petrol/ethyl acetate, 9:1); 0.92; ν_{\max} (neat)/ cm^{-1} ; 2981, 2932, 2868 (C-H), 1715 (C=O), 1642 (C=C), 1148 (C-O); δ_H (300 MHz; CDCl_3), 5.62-5.49 (2H, m, *CHCH*), 3.52 (2H, t, J 6.6 Hz, ClCH_2), 2.99 (2H, d, J 5.5 Hz, CHCH_2CO), 2.08 (2H, q, J 6.9 Hz $\text{CH}_2\text{CH}_2\text{CH}$), 1.77 (2H, quintet, J 7.2 Hz, $\text{ClCH}_2\text{CH}_2\text{CH}_2$), 1.57-1.49 (2H, m, $\text{ClCH}_2\text{CH}_2\text{CH}_2$), 1.44 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_C (75.5 MHz; CDCl_3); 171.3, 132.2, 122.3, 80.6, 45.0, 34.4, 32.1, 28.1, 26.6, 22.7; HRMS (ESI^+) *calcd* for $\text{C}_{12}\text{H}_{21}\text{ClNaO}_2$ $[\text{M}+\text{Na}]^+$ m/z 255.1128 found m/z 255.1113

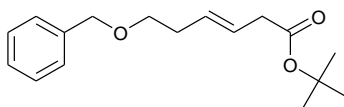
5.14.4 8-Methyl-non-3-enoic acid *tert*-butyl ester (3.90)



Potassium (*E*)-5-methyl-hex-1-enyl-trifluoroborate (**2.116**) (0.159 g, 0.78 mmol) was reacted with *tert*-butyl acrylate (0.050 g, 0.39 mmol) under the standard conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow oil (0.082 g, 93% yield).

R_f (petrol/ethyl acetate, 4:1); 0.71; ν_{\max} (neat)/ cm^{-1} ; 2955, 2929, 2870 (C-H), 1714 (C=O), 1677 (C=C), 1160 (C-O); δ_H (300 MHz; CDCl_3); 5.56-5.24 (2H, m, *CHCH*), 2.99 (2H, d, J 5.7 Hz, CHCH_2CO), 2.05-2.04 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}$), 1.58-1.50 (1H, m, $(\text{CH}_3)_2\text{CH}$), 1.45 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.39-1.28 (2H, m, $\text{CHCH}_2\text{CH}_2\text{CH}_2$), 1.21-1.13 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.88 (6H, app.t, J 6.41 Hz, $(\text{CH}_3)_2\text{CH}$); δ_C (75.5 MHz; CDCl_3); 171.5, 133.2, 121.4, 80.5, 38.6, 34.4, 28.1, 28.0, 27.7, 27.2, 22.7; HRMS (ESI^+) *calcd* for $\text{C}_{14}\text{H}_{26}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ m/z 249.1831 found m/z 249.1841

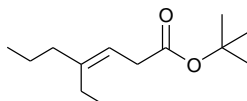
5.14.5 6-Benzyloxy-hex-3-enoic acid *tert*-butyl ester (3.91)



Potassium (*E*)-3-benzyloxy-propenyl-trifluoroborate (**2.120**) (0.198 g, 0.78 mmol) was reacted with *tert*-butyl acrylate (0.050 g, 0.39 mmol) under the standard conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow oil (0.107 g, 99% yield).

R_f (petrol/ethyl acetate, 4:1); 0.5; ν_{\max} (neat)/ cm^{-1} ; 3035, 2980 (C-H), 1726 (C=O), 1148, 1096 (C-O); δ_H (300 MHz; CDCl_3); 7.30-7.20 (5H, m, Ar), 5.65-5.47 (2H, m, *CHCH*), 4.44 (2H, s, ArCH_2O), 3.40 (2H, t, J 6.8 Hz, OCH_2CH_2), 2.95 (2H, d, J 5.4 Hz, COCH_2CH), 2.30 (2H, app.qd, J 6.6, 0.7 Hz, CHCH_2CH_2), 1.37 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_C (75.5 MHz; CDCl_3); 171.1, 138.4, 128.8, 128.3, 127.6, 123.5, 80.5, 72.9, 69.5, 34.4, 28.1, 28.0; HRMS (ESI^+) calcd for $\text{C}_{17}\text{H}_{24}\text{NaO}_3$ $[\text{M}+\text{Na}]^+$ m/z 299.1623 found m/z 299.1615

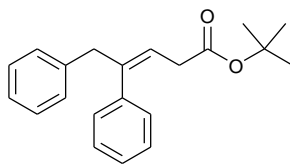
5.14.6 4-Ethyl-hept-3-enoic acid *tert*-butyl ester (3.92)



Potassium (*E*)-1-ethyl-but-1-enyl-trifluoroborate (**2.122**) (0.148 g, 0.78 mmol) was reacted with *tert*-butyl acrylate (0.050 g, 0.39 mmol) under the standard conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow oil (0.030 g, 36% yield).

R_f (petrol/ethyl acetate, 4:1); 0.82; ν_{\max} (neat)/ cm^{-1} ; 3054, 2967, 2934, 2874 (C-H), 1724 (C=O), 1624 (C=C), 1151 (C-O); δ_H (300 MHz; CDCl_3); 5.24 (1H, t, J 7.2 Hz, *CHCH*₂), 2.89 (2H, d, J 8.3 Hz, COCH_2), 2.00-1.89 (4H, m, CH_2CCH_2), 1.37 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.34-1.30 (2H, m, $\text{CH}_3\text{CH}_2\text{CH}_2$), 0.93 (3H, t, J 7.4 Hz, $\text{CH}_3\text{CH}_2\text{C}$), 0.82 (3H, t, J 7.4 Hz, $\text{CH}_3\text{CH}_2\text{CH}_2$); δ_C (75.5 MHz; CDCl_3); 172.3, 147.8, 115.7, 80.7, 39.0, 32.9, 28.5, 23.7, 21.8, 14.5, 13.1

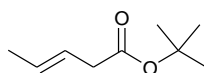
5.14.7 4,5-Diphenyl-pent-3-enoic acid *tert*-butyl ester (3.93)



Potassium (*E*)-1,2-diphenyl-vinyl-trifluoroborate (**2.123**) (0.223 g, 0.78 mmol) was reacted with *tert*-butyl acrylate (0.050 g, 0.39 mmol) under the standard conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow oil (0.125 g, 100% yield).

R_f (petrol/ethyl acetate, 4:1); 0.79; ν_{\max} (neat)/ cm^{-1} ; 3027, 2981 (C-H), 1787 (C=O), 1727 (C=C), 1601 (C=C aryl), 1147 (C-O); δ_H (300 MHz; CDCl_3); 7.40-7.35 (2H, m, *ArH*); 7.24-7.13 (8H, m, *ArH*), 6.17 (1H, t, J 7.3 Hz, CHCH_2), 3.89 (2H, s, ArCH_2), 3.21 (2H, d, J 7.2 Hz, CH_2CO), 1.47 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_C (75.5 MHz; CDCl_3); 171.0, 142.4, 140.1, 139.1, 128.5, 128.3, 128.2, 127.1, 126.5, 126.1, 80.9, 67.2, 36.0, 28.2; HRMS (ESI^+) calcd for $\text{C}_{21}\text{H}_{24}\text{O}_2$ [$\text{M}+\text{H}^+$] m/z 331.1674 found m/z 331.1690

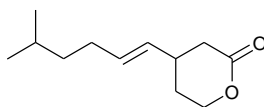
5.14.8 Pent-3-enoic acid *tert*-butyl ester (3.94)



Potassium vinyl trifluoroborate (0.104 g, 0.78 mmol) was reacted with *tert*-butyl acrylate (0.050 g, 0.39 mmol) under the general conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow oil (0.060 g, 98% yield).

R_f (petrol/ethyl acetate, 4:1); 0.76; ν_{\max} (neat)/ cm^{-1} ; 3054, 2985, 2934 (C-H), 1725 (C=O), 1642 (C=C), 1151 (C-O); δ_H (300 MHz; CDCl_3); 5.59-5.46 (2H, m, CHCH), 2.93 (2H, d, J 6.6 Hz, CHCH_2), 1.56 (3H, d, J 6.3 Hz, CHCH_3), 1.38 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_C (75.5 MHz; CDCl_3); 171.7, 127.4, 122.8, 80.8, 34.4, 28.5, 13.3

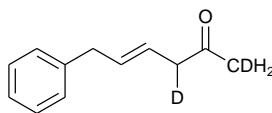
5.14.9 4-(5-Methyl-hex-1-enyl)-tetrahydro-pyran-2-one (3.138)



An oven dried, 24 mL screw-capped vial equipped with a rubber septum was charged with potassium (*E*)-5-methyl-hex-1-enyl-trifluoroborate (**2.116**) (0.208 g, 1.019 mmol), [Rh(OH)(cod)]₂ (0.007 g, 0.0153 mmol), cyclooctadiene (0.0033 g, 0.0306 mmol) and barium hydroxide octahydrate (0.175 g, 1.019 mmol). The reaction vessel was purged with argon and dioxane (1 mL) and water (0.1 mL) were subsequently added by syringe. The reaction was stirred at room temperature for 10 min before addition of 5,6-dihydro-pyran-2-one (0.05 g, 0.51 mmol). The reaction was transferred to a preheated hotplate at 80 °C for 20 h. Upon completion the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution: diethyl ether) and the solvent removed *in vacuo*. Crude product was purified using flash column chromatography on silica gel (eluting with petrol/ethyl acetate 19:1) to afford the title compound as a colourless oil (0.042 g, 42% yield).

R_f (petrol/ethyl acetate, 4:1); 0.35; δ_H (300 MHz; CDCl₃); 5.48 (1H, dt, *J* 15.5, 6.0 Hz, CHCHCH₂), 5.33 (1H, ddt, *J* 15.5, 6.0, 1.1 Hz, CHCHCH), 4.41 (1H, dt, *J* 11.4, 4.7 Hz, OCHH), 4.26 (1H, qd, *J* 9.8, 3.8 Hz, OCHH), 2.66-2.53 (2H, m, COCH₂), 2.30 (1H, td, *J* 15.5, 5.5 Hz, CH₂CH), 2.05-1.88 (2H, m, CH₂CH₂CHCH), 1.73-1.59 (2H, nonet, *J* 4.7 Hz, (CH₃)₂CH), 1.50 (1H, quintet, *J* 6.6 Hz, CHCH(CH₂)₂), 1.26-1.17 (2H, m, CHCH₂CH₂), 0.86 (6H, d, *J* 6.6 Hz); δ_C (75.5 MHz; CDCl₃); 172.2, 132.8, 130.8, 68.5, 40.6, 38.6, 38.5, 30.4, 29.2, 27.5, 22.5; HRMS (*ESI*⁺) *calcd* for C₁₂H₂₀NaO₂ [M+Na]⁺ *m/z* 219.1361 found *m/z* 219.1354

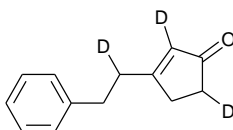
5.14.10 Deuterium labelled isomers of 6-Phenyl-hex-4-en-2-one (3.170)



Potassium (*E*)-styryl trifluoroborate salt (**2.117**) (0.30 g, 1.43 mmol) was reacted with methyl vinyl ketone (0.05 g, 0.71 mmol) in dioxane/D₂O (2.3 mL:1.76 mL) under olefin transposition conditions. The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a mixture of deuterated isomers, as pale yellow oil (0.083 g, 67% yield)

R_f (petrol/ethyl acetate, 4:1); 0.58; δ_H (300 MHz; $CDCl_3$); 7.39-7.29 (2H, m, ArH), 7.23-7.16 (3H, m, ArH), 5.87-5.77 (1H, m, ArCH₂CH), 5.72-5.64 (1H, m, CHCH₂CO), 3.41 (2H, d, J 6.9 Hz, ArCH₂), 3.30 (0.4H, d, J 6.8 Hz, CH₂CO), 2.65-2.60 (0.3H, m, CHDCO), 2.18 (2H, s, CH₃), 2.14 (1H, d, J 8.5 Hz, CH₂D), δ_D (61 MHz; $CDCl_3$); 2.65-2.60 (CD_2 CO, CDHCO), 2.14 (COCH₂D); δ_C (75.5 MHz; $CDCl_3$); 206.6, 133.8, 130.3, 129.9, 129.2, 128.6, 128.4, 42.4, 33.7, 29.7

5.14.11 Deuterated isomers of 3-Phenethyl-cyclopent-2-enone (3.188)

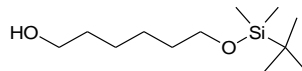


Potassium (*E*)-styryl trifluoroborate salt (**2.117**) (0.256 g, 1.22 mmol) was reacted with cyclopentenone (0.051 mL, 0.609 mmol) in dioxane/D₂O (2 mL:1.5 mL) under olefin transposition conditions. Crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a mixture of deuterated isomers, as a colourless oil (0.074 mg, 64% yield).

R_f (petrol/ethyl acetate, 4:1); 0.55; δ_H (300 MHz; $CDCl_3$); 7.33-7.28 (2H, m, ArH), 7.24-7.18 (3H, m, ArH), 5.98 (0.5H, q, J 1.6 Hz, CHCO), 2.94-2.88 (2H, m, ArCH₂), 2.77-2.70 (1.2H, m, ArCH₂CH₂), 2.59-2.57 (2H, m, COCH₂CH₂), 2.52-2.48 (0.2H, m, COCHD), 2.42-2.36 (0.5H, m, COCH₂); δ_D (61 MHz; $CDCl_3$); 6.04 (CDCO), 2.74 (ArCH₂CHD), 2.39 (COC DH); δ_C (75.5 MHz; $CDCl_3$); 210.0, 181.8, 140.6, 129.9, 128.7, 128.2, 126.4, 35.4, 35.1, 33.4, 31.8

5.15 Synthesis of dihydropyranones

5.15.1 6-(*tert*-Butyl-dimethyl-silanyloxy)-hexan-1-ol (**4.69**)

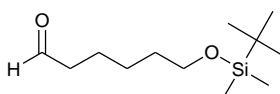


To a solution of 1,6-hexanediol (5.0 g, 42.3 mmol) in anhydrous THF (80 mL) was added triethylamine (6.2 mL, 44.33 mmol), dimethylaminopyridine (0.148 g, 1.2 mmol) and *tert*-butyldimethylsilyl chloride (5.40 g, 35.83 mmol). The reaction mixture was stirred at room temperature for 18 h and then quenched by the addition of water (25 mL). THF was evaporated under reduced pressure and the residue extracted with diethyl ether (3 x 35 mL). Combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 4:1) to afford the title compound as a colourless oil (7.82 g, 94% yield).

R_f (petrol/ethyl acetate, 4:1); 0.4; ν_{\max} (neat)/cm⁻¹; 3342 (br.) (O-H), 2930, 2858 (C-H), 1254 (C-O), 1094 (O-Si), 833 (SiMe₃); δ_{H} (300 MHz; CDCl₃); 3.64 (2H, t, *J* 6.5 Hz, OCH₂), 3.60 (2H, t, *J* 6.5 Hz, OCH₂), 1.62-1.48 (4H, m, OCH₂(CH₂)₂CH₂O), 1.38-1.33 (4H, m, OCH₂(CH₂)₂CH₂O), 0.89 (9H, s, C(CH₃)₃), 0.04 (6H, s, Si(CH₃)₂); δ_{C} (75.5 MHz; CDCl₃); 63.3, 63.1, 32.9, 26.1, 25.7, 25.6, -5.2

All data in accordance with literature values²⁹

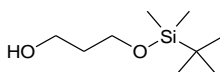
5.15.2 6-(*tert*-Butyl-dimethyl-silanyloxy)-hexanal (**4.65**)



In a dry, argon flushed flask, 6-(*tert*-butyl-dimethyl-silanyloxy)-hexan-1-ol (**4.69**) (7.50 g, 32.27 mmol) was dissolved in anhydrous dichloromethane (200 mL). The solution was cooled to -78 °C and anhydrous DMSO (5.0 mL, 70.98 mmol) added followed by slow addition of oxalylchloride (3.05 mL, 35.49 mmol). The milky white solution was stirred at -78 °C for 45 min before triethylamine (22.64 mL, 161.33 mmol) was added. After 10 min the cooling bath was removed and the reaction warmed to room temperature. After stirring for 30 min the reaction was quenched by the addition of water (50 mL). The layers were separated and the aqueous layer extracted with petroleum

ether (3 x 30 mL). Combined organic layers were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 10:1) to afford the title compound as a pale yellow oil (5.0 g, 67% yield) which was stored under N₂ at -20 °C. R_f (petrol/ethyl acetate, 4:1); 0.55; ν_{\max} (neat)/cm⁻¹; 2930, 2858 (C-H), 1712 (C=O), 1253 (C-O), 1095 (O-Si), 833 (SiMe₃); δ_{H} (300 MHz; CDCl₃); 9.76 (1H, t, *J* 1.7 Hz, COH), 3.60 (2H, t, *J* 6.3 Hz, CH₂OSi), 2.43 (2H, td, *J* 7.3, 1.7 Hz, CH₂COH), 1.70-1.60 (2H, m, CH₂CH₂COH), 1.58-1.49 (2H, m, CH₂CH₂OSi), 1.42-1.30 (2H, m, (CH₂)₂CH₂(CH₂)₂), 0.88 (9H, s, SiC(CH₃)₃), 0.04 (6H, s, Si(CH₃)₂); δ_{C} (75.5 MHz; CDCl₃); 202.8, 62.9, 44.0, 32.6, 26.0, 25.7, 25.5, 22.0, -3.5, -5.2
All data in accordance with literature values²⁹

5.15.3 3-(*tert*-Butyl-dimethyl-silanyloxy)-propan-1-ol (4.70)

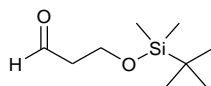


To a solution of 1,3-propanediol (2.5 g, 35 mmol) in anhydrous THF (60 mL) was added triethylamine (5.5 mL, 35.5 mmol), dimethylaminopyridine (0.203 g, 1.66 mmol) and *tert*-butyldimethylsilylchloride (5.0 g, 33.17 mmol). The reaction mixture was stirred at room temperature for 18 h and then quenched by the addition of water (20 mL). THF was evaporated under reduced pressure and the residue extracted with diethyl ether (3 x 35 mL). Combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (3.9 g, 62% yield).

R_f (petrol/ethyl acetate, 4:1); 0.46; ν_{\max} (neat)/cm⁻¹; 3324 (O-H), 2954, 2930, 2858, 2885 (C-H), 1253, 833 (SiMe₃), 1062 (O-Si); δ_{H} (300 MHz; CDCl₃); 3.83 (2H, t, *J* 5.6 Hz, OCH₂), 3.80 (2H, t, *J* 5.5 Hz, OCH₂), 1.77 (2H, quintet, *J* 5.5 Hz, CH₂CH₂CH₂), 0.90 (9H, s, SiC(CH₃)₃), 0.07 (6H, s, Si(CH₃)₂); δ_{C} (75.5 MHz; CDCl₃); 63.0, 62.5, 34.3, 25.9, -5.4

All data in accordance with literature values³⁰

5.15.4 3-(*tert*-Butyl-dimethyl-silanyloxy)-propionaldehyde (4.66)

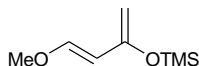


In a dry, argon flushed flask, 3-(*tert*-butyl-dimethyl-silanyloxy)-propan-1-ol (**4.70**) (3.5 g, 18.4 mmol) was dissolved in anhydrous dichloromethane (110 mL). The solution was cooled to -78 °C and anhydrous DMSO (2.88 mL, 40.5 mmol) added followed by slow addition of oxalylchloride (1.74 mL, 20.25 mmol). The milky white solution was stirred at -78 °C for 45 min before triethylamine (12.9 mL, 92 mmol) was added. After 10 min the cooling bath was removed and the reaction warmed to room temperature. After stirring for 30 min the reaction was quenched by the addition of water (35 mL). The layers were separated and the aqueous layer extracted with petroleum ether (3 x 30 mL). Combined organic layers were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 10:1) to afford the title compound as a pale yellow oil (1.76 g, 51% yield) which was stored under N₂ at -20 °C.

R_f (petrol/ethyl acetate, 10:1); 0.15; δ_H (300 MHz; CDCl₃); 9.80 (1H, t, *J* 2.1 Hz, COH), 3.99 (2H, t, *J* 6.0 Hz, CH₂OSi), 2.60 (2H, td, *J* 6.0, 2.1 Hz, CH₂COH), 0.88 (9H, s, SiC(CH₃)₃) 0.06 (6H, s, Si(CH₃)₂); δ_C (75.5 MHz; CDCl₃); 202.3, 57.5, 47.7, 30.3, 25.9, -5.4,

All data in accordance with literature values³⁰

5.15.5 (3-Methoxy-1-methylene-allyloxy)-trimethyl-silane (Danishefsky's Diene) (4.12)



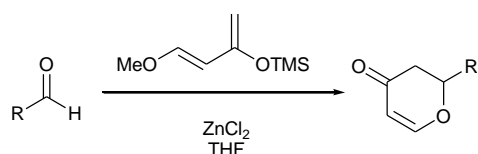
To a solution of triethylamine (30.6 mL, 219.7 mmol) was added anhydrous powder ZnCl₂ (0.408 g, 2.996 mmol) and the reaction mixture stirred at room temperature for 1 h. To this homogeneous solution was added a solution of (*E*)-4-methoxybut-3-en-2-one (10.18 mL, 99.88 mmol) in benzene (40mL), followed by addition of trimethylsilyl chloride (25.0 mL, 199.8 mmol) within 30 min. The reaction was stirred at 40 °C for 24 h, then cooled to room temperature and quenched with addition of dry diethyl ether (150 mL). The formed mixture was filtered through an alumina pad (elution: diethyl ether).

Several filtrations may be required to ensure complete removal of white precipitate. The filtrate was concentrated under vacuum to give the title compound as a red oil (15.0 g, 87% yield) which was stored under N₂ at 5 °C.

δ_{H} (300 MHz; CDCl₃); 6.83 (1H, d, *J* 12.3 Hz, CHOCH₃), 5.53 (1H, d, *J* 12.4 Hz, CCH), 4.09 (2H, d, *J* 12.4 Hz, CH₂), 3.58 (3H, s, OCH₃), 0.23 (9H, s, Si(CH₃)₃); δ_{C} (75.5 MHz; CDCl₃); 154.0, 150.4, 103.2, 91.2, 56.5, 0.1

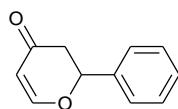
All data in accordance with literature values³¹

5.15.6 General procedure for the synthesis of racemic dihydropyranones



To a flame dried flask under an atmosphere of argon was added ZnCl₂ (0.039 g, 0.28 mmol, 3 mol%) and anhydrous diethyl ether (0.4 mL, 3 mol%). Anhydrous THF (100 mL) was added followed by freshly purified aldehyde (9.42 mmol, 1.0 eq). The reaction was stirred for 10 min before dropwise addition of Danishefsky's Diene (**4.12**) (2.7 mL, 14.13 mmol, 1.5 eq). The reaction was stirred overnight at room temperature and then filtered through celite and concentrated. The crude product was purified by flash column chromatography on silica gel to afford the respective dihydropyranones.

5.15.7 2-Phenyl-2,3-dihydro-pyran-4-one (**4.8**)



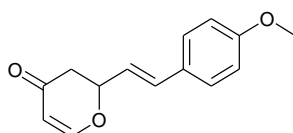
Freshly distilled benzaldehyde (0.96 mL, 9.42 mmol) was reacted under the standard procedure and the crude product purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 8:2) to afford the title compound as a red oil (1.2 g, 73 % yield).

R_f (petrol/ethyl acetate, 7:3); 0.29; ν_{max} (neat)/cm⁻¹; 3063 (C-H), 1722 (C=O), 1670 (C=C), 1593, 1583 (C=C), 1268, 1037 (C-O); δ_{H} (300 MHz; CDCl₃); 7.48 (1H, dd, *J* 6.0, 0.5 Hz, OCH), 7.44-7.35 (5H, m, ArH), 5.52 (1H, dd, *J* 6.0, 1.3 Hz, CHCO), 5.43 (1H, dd, *J* 14.4, 3.5 Hz, CH₂CHAr), 2.91 (1H, dd, *J* 16.9, 14.3 Hz, COCHH), 2.66 (ddd,

J 16.9, 3.5, 1.3 Hz, COHH); δ_C (75.5 MHz; CDCl_3); 192.1, 163.2, 137.9, 129.0, 128.9, 126.2, 107.4, 81.1, 43.4; HRMS (ESI^+) *calcd* for $\text{C}_{11}\text{H}_{10}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ m/z 197.0579 found m/z 197.0590

All data in accordance with literature values³²

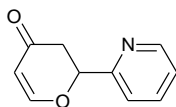
5.15.8 2-[2-(4-Methoxy-phenyl)-vinyl]-2,3-dihydro-pyran-4-one (4.47)



Recrystallised 4-methoxycinnamaldehyde (1.0 g, 6.17 mmol) was reacted under the standard procedure and the crude product purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 8:2) to afford the title compound as an orange solid (0.28 g, 20% yield).

R_f (petrol/ethyl acetate, 4:1); 0.29; ν_{max} (neat)/ cm^{-1} ; 3066, 3009, 2961, 2938, 2909, 2834 (C-H), 1671 (C=O), 1659, 1651 (C=C), 1604, 1587, 1577 (aryl C=C), 1268, 1252, 1205, 1177, 1132, 1033 (C-O); δ_H (300 MHz; CDCl_3); 7.40 (2H, d, J 6.0 Hz, ArH), 7.34 (1H, d, J 8.5 Hz, OCHCH), 6.87 (2H, d, J 8.5 Hz, ArH), 6.70 (1H, d, J 15.9 Hz, ArCHCH), 6.16 (1H, dd, J 15.9, 6.8 Hz, ArCHCH), 5.46 (1H, d, J 6.0 Hz, COCH), 5.07-5.00 (1H, m, CH_2CHO), 3.81 (3H, s, OCH_3), 2.78-2.56 (2H, m, CH_2CO); δ_C (75.5 MHz; CDCl_3); 192.2, 163.2, 150.0, 133.6, 128.2, 128.1, 122.7, 114.1, 107.3, 80.1, 55.4, 42.1; HRMS (ESI^+) *calcd* for $\text{C}_{14}\text{H}_{15}\text{O}_3$ $[\text{M}+\text{H}]^+$ m/z 231.1016 found m/z 231.1059

5.15.9 2-(2-pyridyl)-2,3-dihydro-4H-pyran-4-one (4.51)

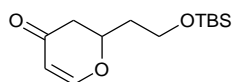


Freshly distilled 2-pyridine carboxaldehyde (1.0 g, 9.336 mmol) was reacted under the standard procedure and the crude product purified by flash column chromatography on silica gel (eluting with dichloromethane/methanol 99:1) to afford the title compound as a red solid (1.004 g, 61% yield).

R_f (petrol/ethyl acetate, 7:3); 0.09; ν_{max} (neat)/ cm^{-1} ; 3078, 3008 (C-H), 1663 (br) (C=O, C=C), 1597, 1584 (C=C), 1273, 1216, 1043 (C-O); δ_H (300 MHz; CDCl_3); 8.62 (1H, d,

J 4.5 Hz, OCHAr), 7.61-7.27 (4H, m, ArH), 5.57-5.51 (2H, m, CH,CH), 3.01 (1H, dd, J 17.0, 13.3 Hz, COCHH), 2.86 (1H, dd, J 17.0, 13.3 Hz, COCHH); δ_{C} (75.5 MHz; CDCl_3); 191.6, 162.4, 156.7, 149.5, 137.1, 123.6, 120.8, 107.8, 81.1, 41.6
All data in accordance with literature values³³

5.15.10 2-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2,3-dihydro-pyran-4-one (4.56)

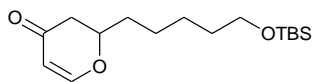


The standard procedure was followed using 3-(*tert*-butyl-dimethyl-silanyloxy)-propionaldehyde (**4.67**) (1.0 g, 9.336 mmol) and the crude product purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 4:1) to afford the title compound as a yellow oil (0.400 g, 39% yield).

R_{f} (petrol/ethyl acetate, 4:1); 0.51; ν_{max} (neat)/ cm^{-1} ; 2954, 2929, 2857 (C-H), 1679 (C=O), 1595 (C=C), 1253, 1273, 1213 (C-O), 1089 (O-Si), 834 (SiMe_3); δ_{H} (300 MHz; CDCl_3); 7.35 (1H, d, J 6.0 Hz, OCH), 5.41 (1H, dd, J 6.0, 1.0 Hz, CHCO), 4.67-4.57 (1H, m, OCHCH_2), 3.85-3.71 (2H, m, OCH_2), 2.63-2.43 (2H, m, COCH_2), 2.07-1.96 (1H, m, CHCHHCH_2), 1.90-1.79 (1H, m, CHCHHCH_2), 0.89 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.05 (6H, s, $\text{Si}(\text{CH}_3)_2$); δ_{C} (75.5 MHz; CDCl_3); 192.7, 163.2, 107.2, 58.4, 42.1, 37.4, 26.0, 18.4, -5.32, -5.36; HRMS (ESI^+) *calcd* for $\text{C}_{13}\text{H}_{25}\text{O}_3$ $[\text{M}+\text{H}]^+$ m/z 257.1572 found m/z 257.1536

All data in accordance with literature values³⁴

5.15.11 2-[5-(*tert*-Butyl-dimethyl-silanyloxy)-pentyl]-2,3-dihydro-pyran-4-one (4.60)

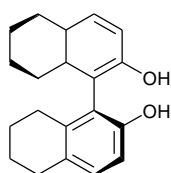


Following the standard procedure 6-(*tert*-butyl-dimethyl-silanyloxy)-hexanal (**4.65**) (1.0 g, 4.09 mmol) was reacted and the crude product purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow oil (0.990 g, 81% yield).

R_{f} (petrol/ethyl acetate, 4:1); 0.56; ν_{max} (neat)/ cm^{-1} ; 2931, 2858 (C-H), 1738 (C=O), 1680 (C=C), 1272, 1250, 1230 (C-O), 1095 (O-Si), 834 (SiMe_3); δ_{H} (300 MHz; CDCl_3);

7.35 (1H, d, J 5.9 Hz, CHCHO), 5.39 (1H, dd, J 5.9, 1.0 Hz, CHCHO), 4.39 (1H, ddt, J 12.7, 7.7, 4.6 Hz, CH₂CHCH₂), 3.61 (2H, t, J 6.3 Hz, CH₂OSi), 2.52 (1H, dd, J 16.7, 12.9 Hz, COCHH), 2.42 (1H, ddd, J 16.7, 4.3, 1.0 Hz, COCHH), 1.89-1.64 (2H, m, CHCH₂CH₂), 1.58-1.49 (2H, m, CH₂CH₂OSi), 1.48-1.33 (4H, m, (CH₂)₂(CH₂)₂OSi), 0.89 (9H, s, SiC(CH₃)₃), 0.04 (6H, s, Si(CH₃)₂); δ_C (75.5 MHz; CDCl₃); 192.9, 163.4, 107.0, 79.6, 63.0, 41.9, 34.5, 32.7, 26.0, 25.7, 24.7, 18.4, -5.2; HRMS (ESI^+) *calcd* for C₁₆H₃₀O₃Si [M+H]⁺ m/z 299.2037 found: m/z 299.2052

5.15.12 (S)-2,2'-dihydroxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl ((S)-H₈-BINOL) (4.73)

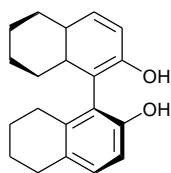


(S)-BINOL (3.0 g 10.47 mmol) and palladium on carbon (0.45 g, 0.52 mmol) were stirred in ethanol (15 mL) under 80 bar H_{2(g)} at 100 °C for 6 h. After cooling to room temperature the reaction mixture was filtered through celite and washed with ethanol. Combined filtrates were concentrated *in vacuo* and purified by flash column chromatography on silica gel (eluting with hexane/diethyl ether 2:1) to afford the title compound as a white crystalline solid (2.5 g, 81% yield).

R_f (hexane/diethyl ether, 2:1); 0.57; ν_{max} (neat)/cm⁻¹; 3475, 3383 (O-H), 2928, 2856 (C-H), 1586, 1472 (C=C aryl), 1152 (C-O); δ_H (300 MHz; CDCl₃); 7.05 (2H, d, J 8.3 Hz, ArH), 6.82 (2H, d, J 8.3 Hz, ArH), 4.65 (2H, br.s, OH), 2.75 (4H, t, J 6.0 Hz, CH₂CCCCCH₂), 2.29 (2H, dt, J 17.8, 6.4 Hz, CH₂CCH), 2.15 (2H, dt, J 17.3, 6.2 Hz, CH₂CCH), 1.78-1.63 (8H, m, 2CH₂(CH₂)CH₂); δ_C (75.5 MHz; CDCl₃); 151.4, 137.2, 131.0, 130.1, 118.9, 113.0, 29.3, 27.1, 23.0; HPLC; Diacel Chiracel OD-H, hexane/propan-2-ol (20:1) 0.5 mL min⁻¹, t_R = 15.1 (minor) and 17.9 min (major)

All data in accordance with literature values³⁵

5.15.13 (R)-2,2'-dihydroxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl ((R)-H₈-BINOL) (4.73)

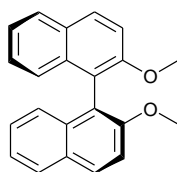


(R)-BINOL (5.0 g, 17.46 mmol) and palladium on carbon (0.75 g, 0.87 mmol) were stirred in ethanol (20 mL) under 80 bar H_{2(g)} at 100 °C for 6 h. After cooling to room temperature the reaction mixture was filtered through celite and washed with ethanol. Combined filtrates were concentrated *in vacuo* and purified by flash column chromatography on silica gel (eluting with hexane/diethyl ether 2:1) to afford the title compound as a white crystalline solid (4.72 g, 80% yield).

R_f (hexane/diethyl ether, 2:1); 0.57; ν_{\max} (neat)/cm⁻¹; 3475, 3383 (O-H), 2928, 2856 (C-H), 1586, 1472 (C=C aryl), 1152 (C-O); δ_{H} (300 MHz; CDCl₃); 7.05 (2H, d, *J* 8.3 Hz, Ar*H*), 6.82 (2H, d, *J* 8.3 Hz, Ar*H*), 4.65 (2H, br.s, OH), 2.75 (4H, t, *J* 6.0 Hz, CH₂CCCCCH₂), 2.29 (2H, dt, *J* 17.8, 6.4 Hz, CH₂CCH), 2.15 (2H, dt, *J* 17.3, 6.2 Hz, CH₂CCH), 1.78-1.63 (8H, m, 2CH₂(CH₂)CH₂); δ_{C} (75.5 MHz; CDCl₃); 151.4, 137.2, 131.0, 130.1, 118.9, 113.0, 29.3, 27.1, 23.0; HPLC; Diacel Chiracel OD-H, hexane/propan-2-ol (20:1) 0.5 mL min⁻¹, t_R = 15.1 (major) and 17.9 min (minor)

All data in accordance with literature values³⁵

5.15.14 (S)-2,2'-Dimethoxy-[1,1']binaphthalenyl (4.74)



A suspension of (S)-BINOL (5.0 g, 17.4 mmol) was heated at 40 °C in anhydrous acetone (150 mL) to give a homogenous solution. To this solution under N₂ was added potassium carbonate (8.0 g, 58.0 mmol) and methyl iodide (5.3 mL, 84.0 mmol). The reaction was refluxed for 24 h then an additional portion of methyl iodide (1.7 mL, 28.0 mmol) was added and the reaction refluxed for an additional 12 h. The solvent was removed under reduced pressure, the residue taken up in water (50 mL) and stirred for 8 h and filtered. The solid was dissolved in dichloromethane (50 mL) and washed with

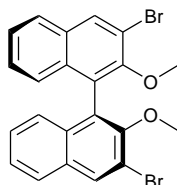
water (25 mL). The aqueous layer was extracted with dichloromethane (25 mL) and combined organic extracts washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure to afford the title compound as pale yellow crystals (5.23 g, 96% yield).

δ_{H} (300 MHz; CDCl₃); 7.98 (2H, d, *J* 9.0 Hz), 7.86 (2H, d, *J* 8.1 Hz), 7.46 (2H, d, *J* 9.0 Hz), 7.31 (2 H, t, *J* 7.3 Hz), 7.21 (2H, t, *J* 7.4 Hz), 7.10 (2H, d, *J* 8.5 Hz), 3.77 (s, 6 H).

δ_{C} (75.5 MHz; CDCl₃); 155.0, 134.0, 131.1, 129.8, 129.4, 128.2, 119.6, 114.2, 56.9.

All data in accordance with literature values^{36,37}

5.15.15 (*S*)-3,3'-Dibromo-2,2'-dimethoxy-[1,1']binaphthalenyl (4.75)

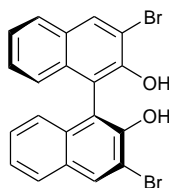


To a solution of TMEDA (1.56 mL, 10.49 mmol) in anhydrous diethyl ether (85 mL) was added ⁿBuLi (5.7 mL, 1.6M in hexanes) at room temperature under an inert atmosphere. The solution was stirred for 15 min and (*S*)-2,2'-dimethoxy-[1,1']binaphthalenyl (**4.74**) (1.50 g, 4.77 mmol) added in one portion. After stirring at room temperature for 3 h, the resulting light brown solution was cooled to -78 °C and bromine (2.9 mL, 57.24 mmol) added over 10 min. The mixture was allowed to warm to room temperature and stirred for 4 h. A saturated solution of Na₂SO_{3(aq)} (20 mL) was added cautiously and the mixture stirred for an additional 4 h. After diluting with diethyl ether (50 mL) and water (50 mL), the organic layer was extracted and washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 8:1) to afford the title compound as a yellow solid (1.27 g, 56% yield).

*R*_f (petrol/ethyl acetate, 4:1); 0.68; *v*_{max} (neat)/cm⁻¹; 2971, 2932, 2884 (C-H), 1160, 1129 (C-O); δ_{H} (300 MHz; CDCl₃); 8.27 (2H, s), 7.83 (2H, d, *J* 8.2 Hz), 7.43 (2H, td, *J* 7.3, 0.9 Hz), 7.27 (2H, td, *J* 7.1, 1.0 Hz), 7.08 (2H, d, *J* 8.6 Hz) 3.51 (6 H, s); HRMS (*ESI*⁺) *calcd* for C₂₂H₁₇Br₂O₂ [M+H]⁺ *m/z* 470.9595 found *m/z* 470.9603

All data in accordance with literature values³⁶

5.15.16 (S)-3,3'-Dibromo-[1,1']binaphthalenyl-2,2'-diol (4.76)

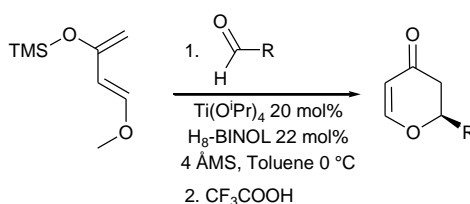


In anhydrous dichloromethane (50 mL) was dissolved (S)-3,3'-dibromo-2,2'-dimethoxy-[1,1']binaphthalenyl (**4.75**) (1.0 g, 2.12 mmol) and the solution cooled to 0 °C. Boron tribromide (11.86 mL, 1M in CH₂Cl₂) was then added dropwise. The mixture was stirred at room temperature for 6 h. The reaction was quenched by the addition of water (20 mL) at 0 °C. The mixture was separated and the aqueous extracted with dichloromethane (2 x 25 mL) and the combined organic extracts washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure to afford the title compound as an orange solid (0.420 g, 45 % yield).

R_f (petrol/ethyl acetate, 4:1); 0.41; ν_{\max} (neat)/cm⁻¹; 3488 (O-H), 3056 (C-H), 1617, 1578, 1498 (C=C aryl), 1135 (C-OH); δ_{H} (300 MHz; CDCl₃); 8.23 (2H, s), 7.81 (2H, d, *J*, 7.7 Hz), 7.23-7.46 (4H, m), 7.08 (2H, d, *J* 7.6 Hz), 5.58 (2H, s); δ_{C} (75.5 MHz; CDCl₃); 152.8, 136.8, 136.5, 133.4, 131.0, 128.4, 119.3, 116.7; HRMS (*ESI*) *calcd* for [M-H]⁻ *m/z* 440.9126 found *m/z* 440.9164

All data in accordance with literature values³⁸

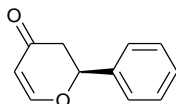
5.15.16 General procedure for the synthesis of chiral dihydropyranones



A mixture of (*R*)-H₈-BINOL (**4.73**) (0.610 g, 2.07 mmol) and Ti(O^{*i*}Pr)₄ (0.56 mL, 1.884 mmol) with activated 4 Å molecular sieves (4.54 g) in anhydrous toluene (38 mL) under an inert atmosphere was heated at 35 °C for 1 h. The yellow mixture was cooled to room temperature and freshly distilled aldehyde (9.42 mmol, 1.0 eq) added. After stirring for 10 min the mixture was cooled to 0 °C and Danishefsky's diene (**4.12**) (11.3 mmol, 1.2 eq) was added. The reaction was stirred at 0 °C for 24 h and then treated with trifluoroacetic acid (0.1 mL). After stirring for a further 15 min at 0 °C, NaHCO₃ (10

mL) was added and the reaction stirred for 10 min and then filtered through a plug of celite. The organic layer was then separated and the aqueous extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to afford the respective dihydropyranones.

5.15.17 (S)-2-Phenyl-2,3-dihydro-pyran-4-one (4.77)

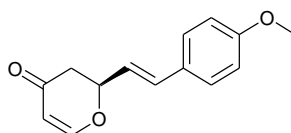


Freshly distilled benzaldehyde (0.96 mL, 9.42 mmol) was reacted under the standard procedure and the crude product purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 8:2) to afford the title compound as a red oil (1.2 g, 73 % yield). The chromatographed material was determined to be in 90% ee by chiral HPLC analysis (Chiralcel OD, 9:1 hexane/propan-2-ol, 1.0 mL min⁻¹, t_R = 11.22 min (major) and 13.23 min (minor).

R_f (petrol/ethyl acetate, 7:3); 0.29; [α]_D²⁰ = +81 (*c*=0.8, CHCl₃); ν_{\max} (neat)/cm⁻¹; 3063 (C-H), 1722 (C=O), 1670 (C=C), 1593, 1583 (C=C), 1268, 1037 (C-O); δ_{H} (300 MHz; CDCl₃); 7.48 (1H, dd, *J* 6.0, 0.6 Hz, OCHCH), 7.44-7.38 (5H, m, ArH), 5.53 (1H, dd, *J* 6.0 Hz, 1.2 Hz, CHCO), 5.43 (1H, dd, *J* 14.4, 3.5 Hz, CH₂CHAr), 2.91 (1H, dd, *J* 17.0, 14.4 Hz, COCHH), 2.66 (1H ddd, *J* 17.0, 3.5, 1.3 Hz, COHH); δ_{C} (75.5 MHz; CDCl₃); 192.2, 163.2, 137.9, 129.0, 128.9, 126.2, 107.5, 81.2, 43.5; HRMS (*ESI*⁺) *calcd* for C₁₁H₁₀NaO₂ [M+Na]⁺ *m/z* 197.0579 found *m/z* 197.0590

All data in accordance with literature values³²

5.15.18 (S)-2-[2-(4-Methoxy-phenyl)-vinyl]-2,3-dihydro-pyran-4-one (4.78)

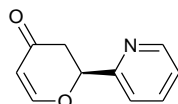


Recrystallised 4-methoxycinnamaldehyde (1.0g, 6.17 mmol) was reacted under the standard procedure and the crude product purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 8:2) to afford the title compound as an orange

solid (0.28 g, 20% yield). The chromatographed material was determined to be in 44% ee by chiral HPLC analysis (Chiralcel ODH, 9:1 hexane/propan-2-ol, 1.0 mL min⁻¹, t_R = 23.59 min (major) and 26.66 min (minor).

R_f (petrol/ethyl acetate, 4:1); 0.29; [α]_D²⁰ = +68 (c=1, CHCl₃); ν_{max} (neat)/cm⁻¹; 3066, 3009, 2961, 2938, 2909, 2834 (C-H), 1671 (C=O), 1659, 1651 (C=C), 1604, 1587, 1577 (aryl C=C), 1268, 1252, 1205, 1177, 1132, 1033 (C-O); δ_H (300 MHz; CDCl₃); 7.40 (2H, d, *J* 6.0 Hz, Ar*H*), 7.34 (1H, d, *J* 8.5 Hz, OCHCH), 6.87 (2H, d, *J* 8.5 Hz, Ar*H*), 6.70 (1H, d, *J* 15.9 Hz, ArCHCH), 6.16 (1H, dd, *J* 15.9, 6.8 Hz, ArCHCH), 5.46 (1H, d, *J* 6.0 Hz, COCH), 5.07-5.00 (1H, m, CH₂CHO), 3.81 (3H, s, OCH₃), 2.78-2.56 (2H, m, CH₂CO); δ_C (75.5 MHz; CDCl₃); 192.2, 163.2, 150.0, 133.6, 128.2, 128.1, 122.7, 114.1, 107.3, 80.1, 55.4, 42.1; HRMS (*ESI*⁺) *calcd* for C₁₄H₁₅O₃ [M+H]⁺ 231.1016 *m/z* found *m/z* 231.1059

5.15.19 (*S*)-2-(2-pyridyl)-2,3-dihydro-4H-pyran-4-one (4.79)

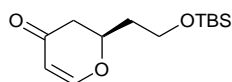


Freshly distilled 2-pyridine carboxaldehyde (1.0 g, 9.336 mmol) was reacted under the standard procedure and the crude product purified by flash column chromatography on silica gel (eluting with dichloromethane/methanol 99:1) to afford the title compound as a red solid (1.004 g, 61% yield). The chromatographed material was determined to be in 14% ee by chiral HPLC analysis (Chiralcel AD, 4:1 hexane/propan-2-ol, 1.0 mL min⁻¹, t_R = 17.02 min (major) and 21.75 min (minor).

R_f (petrol/ethyl acetate, 7:3); 0.09; ν_{max} (neat)/cm⁻¹; 3078, 3008 (C-H), 1663 (br) (C=O, C=C), 1597, 1584 (C=C), 1273, 1216, 1043 (C-O); δ_H (300 MHz; CDCl₃); 8.62 (1H, d, *J* 4.5 Hz), 7.61 -7.27 (4H, m), 5.57-5.51 (2H, m), 3.01 (1H, dd, *J* 17.0, 13.3 Hz), 2.86 (1H, dd, *J* 17.0, 13.3 Hz); δ_C (75.5 MHz; CDCl₃); 191.6, 162.4, 156.7, 149.5, 137.1, 123.6, 120.8, 107.8, 81.1, 41.6

All data in accordance with literature values³³

5.15.20 (S)-2-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2,3-dihydro-pyran-4-one (4.80)

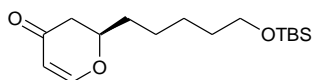


Following the standard procedure 3-(*tert*-butyl-dimethyl-silanyloxy)-propionaldehyde (**4.67**) (1.0 g, 9.336 mmol) was reacted and the crude product purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 4:1) to afford the title compound as a yellow oil (0.400 g, 39% yield). The chromatographed material was determined to be in 62% ee by chiral HPLC analysis (Chiralcel OJ, 99:1 hexane/propan-2-ol, 1.0 mL min⁻¹, t_R = 14.67 min (minor) and 17.31 min (major).

R_f (petrol/ethyl acetate, 4:1); 0.51; [α]_D²⁰ = +31 (c=1.00, CHCl₃); ν_{max} (neat)/cm⁻¹; 2954, 2929, 2857 (C-H), 1679 (C=O), 1595 (C=C), 1253, 1273, 1213 (C-O), 1089 (O-Si), 834 (SiMe₃); δ_H (300 MHz; CDCl₃); 7.35 (1H, d, *J* 6.0 Hz, OCH), 5.41 (1H, dd, *J* 6.0, 1.0 Hz, CHCO), 4.67-4.57 (1H, m, OCHCH₂), 3.85-3.71 (2H, m, OCH₂), 2.63-2.43 (2H, m, COCH₂), 2.07-1.96 (1H, m, CHCHHCH₂), 1.90-1.79 (1H, m, CHCHHCH₂), 0.89 (9H, s, SiC(CH₃)₃), 0.05 (6H, s, Si(CH₃)₂); δ_C (75.5 MHz; CDCl₃); 192.7, 163.2, 107.2, 58.4, 42.1, 37.4, 26.0, 18.4, -5.32, -5.36; HRMS (*ESI*⁺) *calcd* for C₁₃H₂₅O₃ [M+H]⁺ *m/z* 257.1572 found *m/z* 257.1536

All data in accordance with literature values³⁴

5.15.21 (S)-2-[5-(*tert*-Butyl-dimethyl-silanyloxy)-pentyl]-2,3-dihydro-pyran-4-one (4.81)



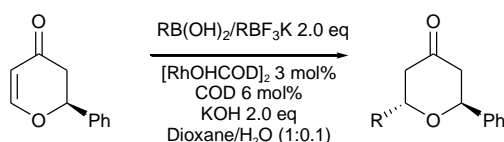
Following the standard procedure 6-(*tert*-butyl-dimethyl-silanyloxy)-hexanal (**4.65**) (1.0 g, 4.09 mmol) was reacted and the crude product purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow oil (0.990 g, 81% yield). The chromatographed material was determined to be in 67% ee by chiral HPLC analysis (Chiralcel ODH, 99:1 hexane/propan-2-ol, 1.0 mL min⁻¹, t_R = 9.31 min (minor) and 10.06 min (major).

R_f (petrol/ethyl acetate, 4:1); 0.56; [α]_D²⁰ = -8 (c=1, CHCl₃); ν_{max} (neat)/cm⁻¹; 2931, 2858 (C-H), 1738 (C=O), 1680 (C=C), 1272, 1250, 1230 (C-O), 1095 (O-Si), 834 (SiMe₃); δ_H (300 MHz; CDCl₃); 7.35 (1H, d, *J* 5.9 Hz, CHCHO), 5.39 (1H, dd, *J* 5.9, 1.0 Hz,

CHCHO), 4.39 (1H, ddt, J 12.7, 7.7, 4.6 Hz, CH_2CHCH_2), 3.61 (2H, t, J 6.3 Hz, CH_2OSi), 2.52 (1H, dd, J 16.7, 12.9 Hz, COCHH), 2.42 (1H, ddd, J 16.7, 4.3, 1.0 Hz, COCHH), 1.89-1.64 (2H, m, CHCH_2CH_2), 1.58-1.49 (2H, m, $\text{CH}_2\text{CH}_2\text{OSi}$), 1.48-1.33 (4H, m, $(\text{CH}_2)_2(\text{CH}_2)_2\text{OSi}$), 0.89 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 0.04 (6H, s, $\text{Si}(\text{CH}_3)_2$); δ_{C} (75.5 MHz; CDCl_3); 192.9, 163.4, 107.0, 79.6, 63.0, 41.9, 34.5, 32.7, 26.0, 25.7, 24.7, 18.4, -5.2; HRMS (ESI^+) calcd for $\text{C}_{16}\text{H}_{30}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ m/z 299.2037 found m/z 299.2052

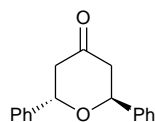
5.16 Rhodium catalysed conjugate additions to dihydropyranones

5.16.1 General procedure for rhodium catalysed conjugate additions to dihydropyranones



An oven dried, 24 mL screw-capped vial equipped with a rubber septum was charged with organoboron reagent (0.228 mmol, 2.0 eq), $[\text{Rh(OH)(cod)}]_2$ (0.0016 g, 0.00342 mmol, 3 mol%), cyclooctadiene (0.007 g, 0.00684 mmol) and potassium hydroxide (0.009 g, 0.228 mmol). The reaction vessel was purged with argon and dioxane (0.5 mL) and water (0.05 mL) were subsequently added by syringe. The red solution was stirred for 15 minutes at room temperature, before the addition of dihydropyranone (0.114 mmol, 1.0 eq). The reaction was transferred to a preheated hotplate at 80 °C for 20 h. Upon completion, the crude reaction mixture was taken up in diethyl ether (5 mL) and filtered through a short plug of silica (elution: diethyl ether) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography on silica gel to afford the desired compounds.

5.16.2 (2S,6S)-Diphenyl-tetrahydro-pyran-4-one (4.83)

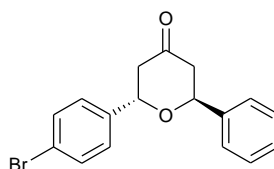


Benzene boronic acid (0.210 g, 1.72 mmol) was reacted with (S)-2-phenyl-2,3-dihydro-pyran-4-one (**4.8**) (0.150 g, 0.86 mmol) under the standard conditions. The crude residue was purified by flash column chromatography on silica gel (eluting with

petrol/ethyl acetate 9:1) to afford the title compound as a white solid (0.207 g, 96% yield).

R_f (petrol/ethyl acetate, 4:1); $[\alpha]_D^{20} = -16$ ($c=1.00$, CHCl_3); 0.47; ν_{max} (neat)/ cm^{-1} ; 3067, 3066, 2974, 2886 (C-H), 1714 (C=O), 1601 (C=C aryl), 1133 (C-O); δ_H (300 MHz; CDCl_3); 7.27-7.26 (10H, m, ArH), 7.05 (2H, m, CHOCH), 6.87 (2H, dd, J 14.6, 6.6 Hz, CHHCOCHH), 6.81 (2H, dd, J 15.0, 5.0 Hz, CHHCOCHH); δ_C (75.5 MHz; CDCl_3); 206.8, 139.9, 128.8, 128.2, 126.8, 73.6, 46.4; HRMS (ESI^+) *calcd* for $\text{C}_{17}\text{H}_{16}\text{NaO}_2$ $[M+\text{Na}]^+$ m/z 275.1048 found: m/z 275.1029; HPLC (Chiralcel ODH, 97:3 hexanes/propan-2-ol, 0.5 mL min^{-1} , t_R = 11.07 min (major) and 13.11 min (minor).

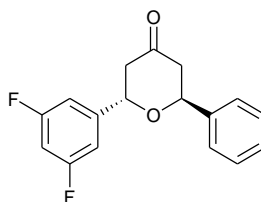
5.16.3 (2*S*,6*S*)-2-(4-Bromo-phenyl)-6-phenyl-tetrahydro-pyran-4-one (4.84)



Under the standard conditions 4-bromophenyl boronic acid (0.058 g, 0.287 mmol) was reacted with (*S*)-2-phenyl-2,3-dihydro-pyran-4-one (**4.8**) (0.025 g, 0.144 mmol). The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (0.044 g, 93% yield).

R_f (petrol/ethyl acetate, 4:1); 0.61; $[\alpha]_D^{20} = -39$ ($c=1.00$, CHCl_3); ν_{max} (neat)/ cm^{-1} ; 2983, 2896 (C-H), 1719 (C=O), 1596, 1494 (C=C aryl), 1245, 1231 (C-O); δ_H (300 MHz; CDCl_3); 7.41 (2H, d, J 7.9 Hz, ArH), 7.30-7.24 (5H, m, ArH), 7.17 (2H, d, J 8.3 Hz, ArH), 5.04 (1H, t, J 5.8 Hz, ArCHO), 4.98 (1H, t, J 5.9 Hz, ArCHO), 2.85 (1H, dd, J 14.8, 6.5 Hz, CHHCOCHH), 2.76 (1H, dd, J 14.8, 5.8 Hz, CHHCOCHH), 2.75 (2H, d, J 6.8 Hz, CHHCOCHH); δ_C (75.5 MHz; CDCl_3); 206.3, 139.6, 139.0, 131.9, 128.8, 128.5, 128.3, 126.8, 122.2, 73.8, 72.9, 46.9, 46.3; HRMS (ESI^+) *calcd* for $\text{C}_{17}\text{H}_{15}\text{BrNaO}_2$ $[M+\text{Na}]^+$ m/z 353.0153 found: m/z 252.0124; HPLC (Chiralcel OJ, 9:1 hexane/propan-2-ol, 1.0 mL min^{-1} , t_R = 20.36 min (minor) and 28.61 min (major).

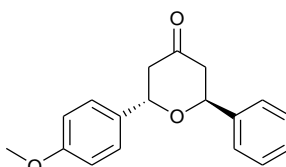
5.16.4 (2*S*,6*S*)-2-(3,5-Difluoro-phenyl)-6-phenyl-tetrahydro-pyran-4-one (4.85)



Under the standard conditions 3,5-difluorophenylboronic acid (0.045 g, 0.287 mmol) was reacted with (*S*)-2-phenyl-2,3-dihydro-pyran-4-one (**4.8**) (0.025 g, 0.144 mmol). The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow solid (0.038 g, 92% yield).

R_f (petrol/ethyl acetate, 4:1); 0.6; $[\alpha]_D^{20} = -19$ ($c=1.00$, CHCl_3); δ_H (300 MHz; CDCl_3); 7.42-7.30 (5H, m, *ArH*), 6.90 (2H, ddd, J 8.2, 2.2, 0.7 Hz, FCHCHCF), 6.75 (1H, tt, J 8.8, 2.3 Hz, CFCHCF), 5.34 (1H, t, J 5.7 Hz, *OCH*), 4.97 (1H, dd, J 6.82, 5.64 Hz, *OCH*), 2.93 (2H, ddd, J 14.5, 5.7, 0.9 Hz, CHHCOCHH), 2.85-2.72 (2H, m, CHHCOCHH); δ_C (75.5 MHz; CDCl_3); 205.7, 144.2, 139.2, 128.9, 128.5, 127.0, 109.5 (d, J 30 Hz), 103.5, 74.2, 72.3, 46.8, 45.8; HPLC (Chiralcel AD: 99:1 hexanes/propan-2-ol, 0.5 mL min⁻¹, t_R = 37.30 min (major) and 48.68 min (minor).

5.16.5 (2*S*,6*S*)-2-(4-Methoxy-phenyl)-6-phenyl-tetrahydro-pyran-4-one (4.86)

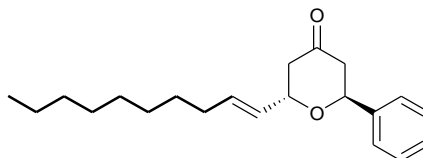


Under the standard conditions 4-methoxyphenylboronic acid (0.035 g, 0.23 mmol) was reacted with (*S*)-2-phenyl-2,3-dihydro-pyran-4-one (**4.8**) (0.020 g, 0.115 mmol). The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as an off white solid (0.029 g, 81% yield).

R_f (petrol/ethyl acetate, 4:1); $[\alpha]_D^{20} = -9$ ($c=0.47$, CHCl_3); 0.52; δ_H (300 MHz; CDCl_3); 7.38-7.29 (5H, m, *ArH*), 7.29 (2H, d, J 8.5, *ArH*), 6.89 (2H, d, J 8.8 Hz, *ArH*), 5.15 (1H, t, J 5.7 Hz, *CHO*), 5.04 (1H, dd, J 7.1, 5.1 Hz, *CHO*), 3.81 (3H, s, OCH_3), 2.97-2.76 (4H, m, CH_2COCH_2); δ_C (75.5 MHz; CDCl_3); 207.1, 159.5, 140.1, 131.9, 128.7,

128.4, 128.2, 126.7, 114.1, 73.5, 73.2, 55.4, 46.8, 46.2; HRMS (ESI^+) *calcd* for $C_{18}H_{18}NaO_3$ $[M+Na]^+$ m/z 305.1154 found m/z 305.1123; HPLC (Chiralcel AD: 98:2 hexanes/propan-2-ol, 1.0 mL min⁻¹, t_R = 20.82 min (major) and 27.07 min (minor))

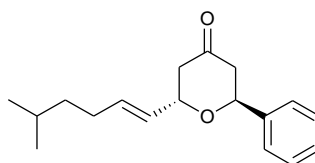
5.16.6 (2*S*, 6*S*)-2-Dec-1-enyl-6-phenyl-tetrahydro-pyran-4-one (4.87)



Potassium decenyl trifluoroborate salt (**2.114**) (0.057 g, 0.23 mmol) was reacted with (*S*)-2-phenyl-2,3-dihydro-pyran-4-one (**4.8**) (0.020 g, 0.115 mmol) under the standard conditions. The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow oil (0.025 g, 69% yield).

R_f (petrol/ethyl acetate, 4:1); 0.69; $[\alpha]_D^{20} = -8$ ($c=1.00$, $CHCl_3$); ν_{max} (neat)/cm⁻¹; 3037, 2924, 2854 (C-H), 1720 (C=O), 1667 (C=C), 1603 (C=C aryl), 1249, 1052 (C-O); δ_H (300 MHz; $CDCl_3$); 7.38-7.29 (5H, m ArH), 7.00 (1H, dt, J 15.7, 6.3 Hz, CH_2CH), 5.57 (1H, dd, J 15.7, 4.9 Hz, CH_2CHCH), 5.11 (1H, dd, J 7.4 Hz, 5.4 Hz, ArCHO), 4.71 (1H, dd, J 9.6, 4.7 Hz, $CHCHO$), 2.74 (1H, dd, J 14.4, 5.9 Hz, $CHHCOCHH$), 2.70 (2H, d, J 6.6 Hz, $CHHCOCHH$), 2.60 (1H, dd, J 14.4, 4.6 Hz, $CHHCOCHH$), 2.06 (2H, q, J 6.9 Hz, CH_2CH), 1.35 (2H, dd, J 13.0, 5.9 Hz, CH_2CH_2CH), 1.30-1.22 (10H, m, $CH_3(CH_2)_8$), 0.87 (3H, t, J 6.6 Hz, CH_3); δ_C (75.5 MHz; $CDCl_3$); 206.9, 140.0, 136.0, 128.8, 128.3, 128.1, 126.5, 73.1, 72.9, 48.0, 45.4, 32.5, 31.9, 29.5, 29.4, 29.2, 29.0, 22.8, 14.2; HPLC (Chiralcel ODH: 98:2 hexanes/propan-2-ol, 1.0 mL min⁻¹, t_R = 19.43 min (minor) and 21.42 min (major))

5.16.7 (2*S*, 6*S*)-2-(5-Methyl-hex-1-enyl)-6-phenyl-tetrahydro-pyran-4-one (4.88)

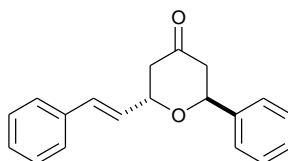


Potassium (*E*)-(5-methyl-hex-1-enyl) trifluoroborate (**2.116**) (0.047 g, 0.23 mmol) was reacted with (*S*)-2-phenyl-2,3-dihydro-pyran-4-one (**4.8**) (0.020 g, 0.115 mmol) under the standard conditions. The crude residue was purified by flash column

chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a yellow oil (0.024 g, 77% yield).

R_f (petrol/ethyl acetate, 4:1); 0.78; $[\alpha]_D^{20} = -6$ ($c=1.00$, CHCl_3); ν_{\max} (neat)/ cm^{-1} ; 3068, 2955, 2870 (C-H), 1706 (C=O), 1648 (C=C), 1602 (C=C aryl), 1268, 1069 (C-O); δ_H (300 MHz; CDCl_3); 7.38-7.27 (5H, m, ArH), 5.69 (1H, dtd, J 15.7, 6.3, 0.9 Hz, CH_2CHCH), 5.57 (1H, dtd, J 15.7, 5.0, 1.0 Hz, CH_2CHCH), 5.11 (1H, dd, J 7.4, 5.3 Hz, ArCHO), 4.70 (1H, dd, J 9.7, 4.8 Hz, CHCHO), 2.76 (1H, dd, J 14.4, 5.7, CHHCOCHH), 2.70 (2H, d, J 5.4 Hz, CHHCOCHH), 2.60 (1H, ddd, J 14.4, 4.6, 1.0 Hz, CHHCOCHH), 2.10-2.03 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}$), 1.53 (1H, nonet, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$), 1.29-1.24 (2H, m, $(\text{CH}_3)_2\text{CHCH}_2$), 0.88 (6H, d, J 6.6 Hz, $(\text{CH}_3)_2\text{CH}$); δ_C (75.5 MHz; CDCl_3); 206.9, 140.5, 136.1, 128.1, 126.4, 73.1, 72.9, 48.0, 45.4, 38.1, 30.4, 27.6, 22.5; HPLC (Chiralcel AD; 98:2 hexanes/propan-2-ol, 1.0 mL min^{-1} , t_R = 6.85 min (major) and 15.91 min (minor))

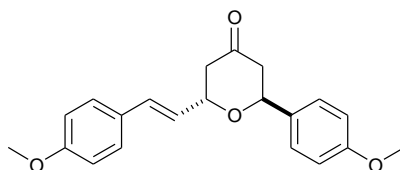
5.16.8 (2*S*,6*S*)-2-Phenyl-6-styryl-tetrahydro-pyran-4-one (4.89)



Potassium (*E*)-styryl trifluoroborate (**2.117**) (0.907 g, 4.32 mmol) was reacted with (*S*)-2-phenyl-2,3-dihydro-pyran-4-one (**4.8**) (0.20 g, 1.148 mmol) under the standard conditions. The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a white solid (0.20 g, 63% yield).

R_f (petrol/ethyl acetate, 4:1); 0.5; $[\alpha]_D^{20} = -77$ ($c=1$, CHCl_3), ν_{\max} (neat)/ cm^{-1} ; 3035, 2979, 2882 (C-H), 1720 (C=O), 1658 (C=C), 1600, 1579 (C=C aryl), 1231, 1048 (C-O); δ_H (300 MHz; CDCl_3); 7.34-7.17 (10H, m, ArH), 6.53 (1H, dd, J 16.3, 1.4 Hz, ArCH), 6.23 (1H, dd, J 16.3, 5.0 Hz, ArCHCH), 5.12 (1H, dd, J 7.4, 5.0 Hz, ArCHO), 4.83 (1H, ddd, J 10.7, 5.2, 1.4 Hz, CHCHO), 2.79-2.63 (4H, m, CH_2COCH_2); δ_C (75.5 MHz; CDCl_3); 206.5, 140.3, 136.0, 133.5, 128.8, 128.7, 128.3, 128.2, 127.8, 126.7, 126.5, 73.6, 72.9, 47.8, 45.4; HRMS (ESI^+) *calcd* for $\text{C}_{19}\text{H}_{18}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ m/z 301.1204 found m/z 301.1177; HPLC (Chiralcel ODH; 95:5 hexanes/propan-2-ol, 1.0 mL min^{-1} , t_R = 13.37 min (major) and 21.93 min (minor))

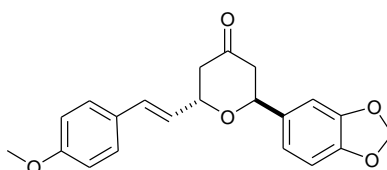
5.16.8 2-(4-Methoxy-phenyl)-6-[2-(4-methoxy-phenyl)-vinyl]-tetrahydro-pyran-4-one (4.91)



Under the standard conditions 4-methoxy phenylboronic acid (0.026 g, 0.174 mmol) was reacted with 2-[2-(4-methoxy-phenyl)-vinyl]-2,3-dihydro-pyran-4-one (**4.47**) (0.020 g, 0.0869 mmol). The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 8:2) to afford the title compound as a yellow oil (0.017 g, 58% yield).

R_f (petrol/ethyl acetate, 4:1); 0.26; ν_{\max} (neat)/ cm^{-1} ; 2935, 2837 (C-H), 1714 (C=O), 1607 (C=C), 1510 (C=C aryl), 1245, 1174, 1029 (C-O); δ_H (300 MHz; CDCl_3); 7.32 (4H, dd, J 8.8, 2.2 Hz, ArH), 6.88 (4H, dd, J 11.6, 8.8 Hz, ArH), 6.52 (1H, d, J 16.2, 5.3 Hz, ArCH), 6.15 (1H, d, J 16.2, 5.3 Hz, ArCHCH), 5.17 (1H, dd, J 7.2, 4.9 Hz, ArCHO), 4.81 (1H, ddd, J 9.4, 5.3, 1.4 Hz, CHCHO), 3.81 (6H, s, OCH_3 , OCH_3), 2.87-2.63 (4H, m, CH_2COCH_2); δ_C (75.5 MHz; CDCl_3); 206.5, 160.0, 150.0, 133.5, 127.9, 127.8, 126.0, 114.1, 73.1, 72.5, 55.3, 47.7, 46.3; HRMS (ESI^+) *calcd* for $\text{C}_{21}\text{H}_{22}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$ m/z 361.1416 found: m/z 361.1404; HPLC (Chiralcel ODH; 95:5 hexanes/propan-2-ol, 1.0 mL min^{-1} , t_R = 26.2 min and 40.5 min

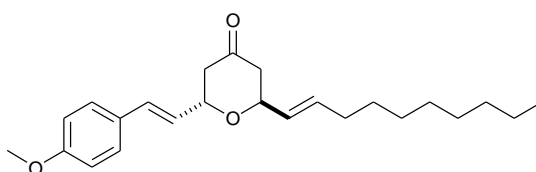
5.16.9 2-Benzo[1,3]dioxol-5-yl-6-[2-(4-methoxy-phenyl)-vinyl]-tetrahydro-pyran-4-one (4.92)



Benzo-[1,3]dioxol-5-ylboronic acid (0.029 g, 0.174 mmol) was reacted with 2-[2-(4-methoxy-phenyl)-vinyl]-2,3-dihydro-pyran-4-one (**4.47**) (0.020 g, 0.0869 mmol) under the standard conditions. The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 8:2) to afford the title compound as a yellow oil (0.032 g, 75% yield).

R_f (petrol/ethyl acetate, 4:1); 0.38; ν_{\max} (neat)/ cm^{-1} ; 2906, 2862 (C-H), 1715 (C=O), 1641 (C=C), 1606, 1577, 1511 (C=C aryl), 1246, 1033 (C-O); δ_H (300 MHz; CDCl_3); 7.33 (3H, d, J 8.8 Hz, ArH), 6.89 (2H, d, J 11.7 Hz, ArH), 6.82 (2H, d, J 11.5 Hz, ArH), 6.53 (1H, d, J 16.2 Hz, ArCHCH), 6.14 (1H, dd, J 16.4, 5.5 Hz, ArCHCH), 5.96 (2H, s, OCH_2O), 5.10 (1H, dd, J 7.0, 5.4 Hz, ArCHO), 4.84 (1H, ddd, J 10.6, 5.3, 1.2 Hz, CHCHO), 3.81 (3H, s, ArOCH_3), 2.83-2.65 (4H, m, CH_2COCH_2); HRMS (ESI^+) *calcd* for $\text{C}_{21}\text{H}_{20}\text{NaO}_5$ $[\text{M}+\text{H}]^+$ m/z 375.1208 found m/z 375.1192; HPLC (Chiralcel ODH; 97:3 hexanes/propan-2-ol, 1.0 mL min^{-1} , t_R = 50.31 min and 84.14 min

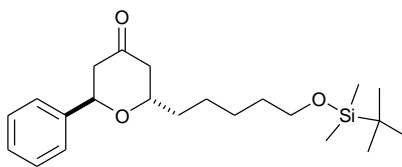
5.16.10 2-Dec-1-enyl-6-[2-(4-methoxy-phenyl)-vinyl]-tetrahydro-pyran-4-one (4.93)



Potassium decenyl trifluoroborate (**2.114**) (0.043 g, 0.174 mmol) was reacted with 2-[2-(4-methoxy-phenyl)-vinyl]-2,3-dihydro-pyran-4-one (**4.47**) (0.020 g, 0.0869 mmol) under the standard conditions. The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethylacetate 8:2) to afford the title compound as a yellow oil (0.026 g, 81% yield).

R_f (petrol/ethyl acetate, 4:1); 0.5; ν_{\max} (neat)/ cm^{-1} ; 2925, 2855 (C-H), 1718 (C=O), 1610, 1514 (C=C aryl), 1250 (C-O); δ_H (300 MHz; CDCl_3); 7.32 (2H, d, J 8.7 Hz, ArH), 6.85 (2H, d, J 8.7 Hz, ArH), 6.53 (1H, d, J 16.1 Hz, ArCHCH), 6.12 (1H, dd, J 16.1, 5.6 Hz, ArCHCH), 5.71 (1H, dt, J 16.0, 6.6 Hz, CH_2CHCH), 5.55 (1H, dd, J 15.7, 5.5 Hz, CH_2CHCH), 4.80 (1H, dd, J 10.7, 5.1 Hz, CHO), 4.67 (1H, dd, J 10.7, 5.6 Hz, CHO), 3.08 (3H, s, OCH_3), 2.69-2.47 (4H, m, CH_2COCH_2), 2.05 (2H, q, J 6.9 Hz, CH_2CHCH), 1.37-1.26 (12H, m, $\text{CH}_3(\text{CH}_2)_6$), 0.88 (3H, t, J 6.6 Hz, $\text{CH}_3(\text{CH}_2)_6$); δ_C (75.5 MHz; CDCl_3); 206.7, 159.9, 135.4, 132.4, 128.6, 127.9, 126.0, 125.7, 114.1, 72.6, 72.5, 55.4, 46.3, 32.5, 32.0, 29.5, 29.3, 29.3, 29.0, 22.8, 14.2; HRMS (ESI^+) *calcd* for $\text{C}_{24}\text{H}_{35}\text{O}_3$ $[\text{M}+\text{H}]^+$ m/z 371.2586 found m/z 371.2588; HPLC (Chiralcel ODH; 95:5 hexanes/propan-2-ol, 1.0 mL min^{-1} , t_R = 8.06 min and 11.32 min

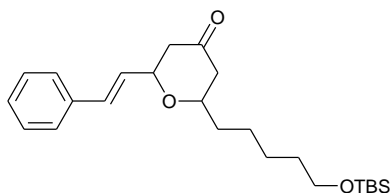
5.16.11 2-[5-(*tert*-Butyl-dimethyl-silanyloxy)-pentyl]-6-phenyl-tetrahydro-pyran-4-one (4.96)



Phenylboronic acid (0.021 g, 0.168 mmol) was reacted with (*S*)-2-[5-(*tert*-butyl-dimethyl-silanyloxy)-pentyl]-2,3-dihydro-pyran-4-one (**4.60**) (0.025 g, 0.0838 mmol) under the standard conditions. The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (0.020 g, 64% yield).

R_f (petrol/ethyl acetate, 4:1); 0.72; δ_H (300 MHz; $CDCl_3$); 7.41-7.28 (5H, m, ArH), 5.21 (1H, t, J 5.7 Hz, ArCHO), 3.98-3.90 (1H, m, OCHCH₂), 3.57 (2H, t, J , 1.56 Hz, CH₂OSi), 2.88-2.74 (2H, m, COCH₂), 2.57 (1H, ddd, J 14.4, 4.5, 1.1 Hz, COCHH), 2.34 (1H, dd, J 14.4, 7.3, 1.1 Hz, COCHH), 1.54-1.40 (4H, m, CH₂CH₂), 1.37-1.27 (4H, m, CH₂CH₂), 0.88 (9H, s, C(CH₃)₃), 0.03 (6H, s, Si(CH₃)₂); δ_C (75.5 MHz; $CDCl_3$); 207.3, 140.2, 128.6, 128.0, 126.8, 63.1, 47.2, 46.2, 34.55, 32.72, 25.9, 25.6, 25.1, 18.4, -5.26

5.16.12 2-[5-(*tert*-Butyl-dimethyl-silanyloxy)-pentyl]-6-styryl-tetrahydro-pyran-4-one (4.97)

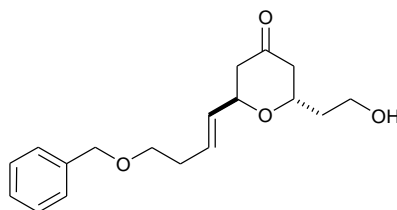


Potassium (*E*)-styryl trifluoroborate (**2.117**) (0.028 g, 0.13 mmol) was reacted with (*S*)-2-[5-(*tert*-butyl-dimethyl-silanyloxy)-pentyl]-2,3-dihydro-pyran-4-one (**4.60**) (0.020 g, 0.067 mmol) under the standard conditions. The crude residue was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 9:1) to afford the title compound as a colourless oil (0.010 g, 37% yield).

R_f (petrol/ethyl acetate, 4:1); 0.62; ν_{max} (neat)/cm⁻¹; 2931, 2858 (C-H), 1713 (C=O), 1623 (C=C), 1579, 1569 (C=C aryl), 1251, 1049 (C-O); δ_H (300 MHz; $CDCl_3$); 7.40-7.27 (5H, ArH), 6.56 (1H, dd, J 16.1, 1.2 Hz, ArCH), 6.23 (1H, dd, J 11.2, 5.2 Hz,

ArCHCH), 4.87 (1H, dd, J 9.6, 4.5 Hz, CHCHO), 4.12-4.03 (1H, m, OCHCH₂), 3.59 (2H, t, J 6.4 Hz, CH₂OTBS), 2.68 (2H, qd, J 14.3, 5.4 Hz, COCH₂), 2.49 (1H, ddd, J 14.2, 4.0, 1.2 Hz, COCHH), 2.29 (1H, dd, J 13.9, 8.2 Hz, COCHH), 1.55-1.46 (4H, m, CH₂CH₂), 1.43-1.34 (4H, m, CH₂CH₂), 0.88 (9H, s, SiC(CH₃)₃), 0.03 (6H, s, Si(CH₃)₂); HPLC (Chiralcel ODH; 95:5 hexanes/propan-2-ol, 1.0 mL min⁻¹, t_R = 6.33 min and 11.35 min

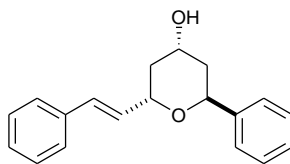
5.16.13 2-(4-Benzyloxy-but-1-enyl)-6-(2-hydroxy-ethyl)-tetrahydro-pyran-4-one (4.98)



Potassium (*E*)-(4-(-benzyloxy)but-1-en-1-yl)trifluoroborate (**2.140**) (0.105 g, 0.39 mmol) was reacted with 2-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-2,3-dihydro-pyran-4-one (**4.56**) (0.050 g, 0.195 mmol) under the standard conditions. The crude residue was treated with TBAF (0.43 mL, 1M in THF) in THF (2mL). After stirring for 1 h, a saturated solution of NH₄Cl was added and the mixture extracted with Et₂O (3 x 10 mL). Combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluting with dichloromethane/methanol 9:1) to afford the title compound as a yellow oil (0.048 g, 81% yield).

R_f (dichloromethane/methanol 9:1); 0.46; ν_{max} (neat)/cm⁻¹; 3342 (O-H), 2930, 2858 (C-H), 1472, 1463 (C=C), 1254, 1094 (C-O); δ_H (300 MHz; CDCl₃); 7.37-7.27 (5H, m, ArH), 5.71 (1H, dt, J 15.8, 6.4 Hz, CH₂CHCH), 5.58 (1H, dd, J 15.8, 4.7 Hz, CH₂CHCH), 4.75 (1H, dd, J 9.7, 4.7 Hz, CHCHO), 4.49 (2H, s, ArCH₂O), 4.26 (1H, m, OCHCH₂), 3.73 (1H, br.s, OH), 3.50 (2H, t, J 6.6 Hz, OCH₂CH₂), 2.67 (1H, dd, J 14.5, 6.2 Hz, CHHCOCHH), 2.52 (1H, ddd, J 14.6, 3.8, 1.4 Hz, CHHCOCHH), 2.43-2.28 (4H, m, CHHCOCHH, CH₂CHCH), 1.91-1.62 (2H, m, OCHCH₂); δ_C (75.5 MHz; CDCl₃); 206.5, 138.3, 132.2, 130.3, 128.4, 127.7, 127.6, 73.0, 72.9, 70.5, 69.2, 60.3, 47.6, 44.9, 37.5, 32.9

5.16.14 2-Phenyl-6-styryl-tetrahydro-pyran-4-ol (4.107)



To a solution of 2-phenyl-6-styryl-tetrahydro-pyran-4-one (**4.89**) (0.045 g, 0.162 mmol) in anhydrous ethylacetate (0.32 mL) under an argon atmosphere was added a solution of 2:5 Et₃N:COOH (0.024 mL). [CymeneRuCl]₂ (0.025 g, 0.00041 mmol) and (R,R)-TosylDPEN (0.003 g, 0.0081 mmol) were dissolved in dichloromethane (0.03 mL) and added to the stirred solution. The reaction was stirred at 50 °C for 48 h. After cooling the reaction was diluted with ethyl acetate (1 mL) and filtered through a short pad of silica (elution: ethyl acetate). After concentration under reduced pressure the crude product was purified by flash column chromatography on silica gel (eluting with petrol/ethyl acetate 7:3) to afford the title compound as a white solid (0.033 g, 77% yield, 8:2 de). The product was recrystallised in ethyl acetate/hexane to afford the desired compound with amplified de (0.018 g, 40% yield, >99% de).

R_f (petrol: ethyl acetate, 4:1); 0.98; $[\alpha]_D^{20} = -36$ (*c*=1, CHCl₃), ν_{\max} (neat)/cm⁻¹; 3351 (O-H), 3027, 2948 (C-H), 1714 (C=C), 1600, 1493 (C=C aryl), 1260, 1045 (C-O); δ_H (300 MHz; CDCl₃); 7.48-7.39 (6H, m, ArH), 7.36-7.28 (4H, m, ArH), 6.64 (1H, d, *J* 16.0 Hz, PhCHCH), 6.36 (1H, dd, *J* 16.0, 5.7 Hz, PhCHCH), 5.31 (1H, t, *J* 4.3 Hz, PhCHO), 4.29-4.24 (1H, m, CHCHO), 4.12-4.03 (1H, m, CHOH), 2.58-2.51 (1H, m, PhCHCHH), 2.11-2.05 (1H, m, PhCHCHH), 2.01-1.91 (1H, m, CHCHCHH), 1.69-1.62 (1H, m, CHCHCHH); δ_C (75.5 MHz; CDCl₃); 140.7, 136.8, 130.6, 130.0, 128.7, 128.6, 127.7, 127.3, 126.6, 126.4, 72.2, 70.6, 64.7, 40.5, 37.0; HPLC (Chiralcel ODH; 97:3 hexanes/propan-2-ol, 0.5 mL min⁻¹, *t_R* = 60.38 min (major) and 109.35 min (minor).

All data in accordance with literature values³⁹

5.17 References

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Appendices

Calibration for Gas Chromatography analysis of the rhodium catalysed conjugate addition reaction.

Calibration curve sample preparation

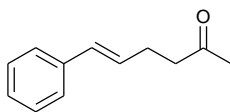
Dihexylether (1 mL, 4.26 mmol) was used as a standard and dissolved in dioxane (3 mL) to afford a 1.42 M stock solution. A number of solutions of each of the following samples over a range of concentrations were made up and an aliquot of the standard stock solution was added to each.

The samples were analysed by GC and the area response recorded. The ratio of the area of sample to standard was calculated and the ratio of sample concentration was calculated. To calculate the Response Factor 'F':

$$\frac{C_{unk}}{C_{std}} = F_{unk} \frac{A_{unk}}{A_{std}}$$

Where C_{unk} = Concentration of unknown, C_{std} = Concentration of standard, A_{unk} = Area of unknown, A_{std} = area of standard. Therefore a plot of C_{unk}/C_{std} against A_{unk}/A_{std} will afford linear plots with gradient = the response factor. To extrapolate the sample concentration from the calibration curve the sample response must be linear throughout the range of concentrations used.

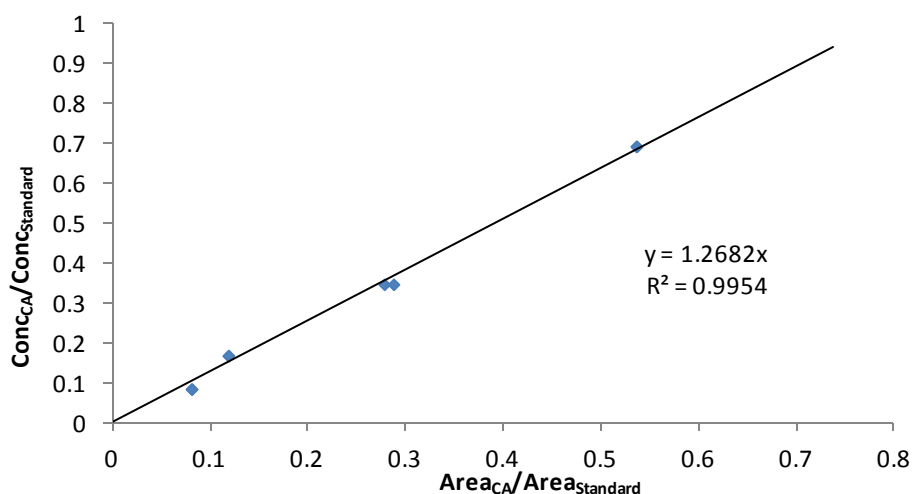
Relative response factor (RRF) for 6-phenyl-hex-5-en-2-one (3.34)



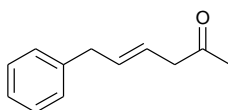
6-Phenyl-hex-5-en-2-one (0.213 g, 0.1225 mmol) was dissolved in dioxane (2 mL). 0.1 mL, 0.2 mL, 0.3 mL, 0.4 mL and 0.5 mL aliquots were taken, and 0.05 mL of the standard stock solution added and each diluted to 1 mL (dioxane) for analysis. Conjugate addition R factor = 1.2682

Entry	[CA]	[Standard]	Area _{CA}	Area _{Standard}	$\frac{Area_{CA}}{Area_{Standard}}$	$\frac{Conc_{CA}}{Conc_{Standard}}$
1	0.0059	0.071	202.8	2465.4	0.082258	0.08309859
2	0.0059	0.071	205.8	2500.3	0.08231	0.08309859
3	0.0071	0.0426	308.5	2573.3	0.119885	0.16666667
4	0.0071	0.0426	302.9	2523.6	0.120027	0.16666667
5	0.0147	0.0426	602.8	2156.2	0.279566	0.34507042
6	0.0147	0.0426	617.8	2137.6	0.289016	0.34507042
7	0.0294	0.0426	1221.8	2273.1	0.537504	0.69014085
8	0.0294	0.0426	1210.6	2250.5	0.537925	0.69014085
9	0.0059	0.071	202.8	2465.4	0.082258	0.08309859
10	0.0059	0.071	205.8	2500.3	0.08231	0.08309859

Relative response factor (RRF) plot for conjugate addition product



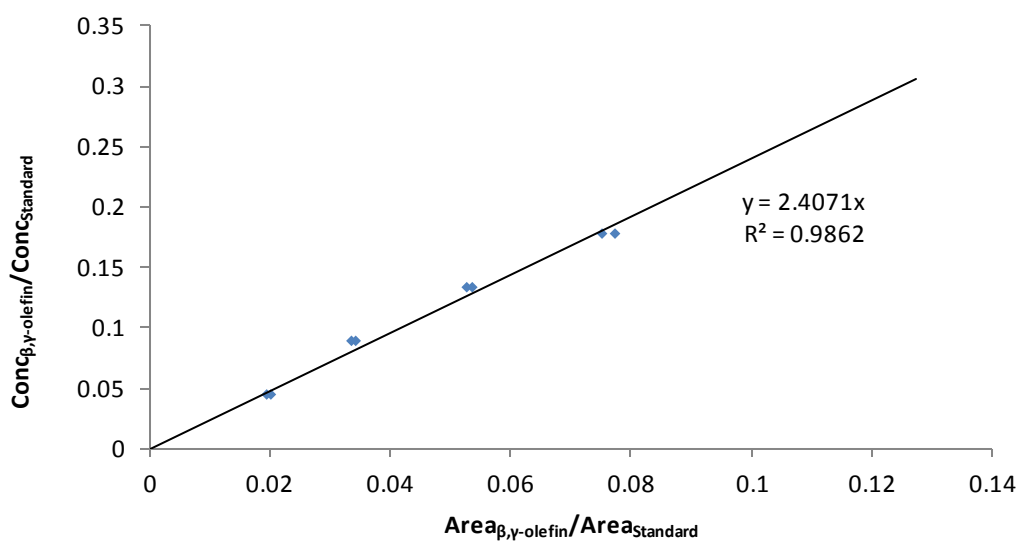
Relative response factor (RRF) for 6-phenyl-hex-4-en-2-one (3.35)



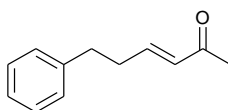
6-Phenyl-hex-4-en-2-one (0.022 g, 0.126 mmol) was dissolved in dioxane (1 mL). 0.1 mL, 0.2 mL, 0.3 mL and 0.4 mL aliquots were taken, 0.2 mL of the standard stock solution was added and each diluted to 1 mL (dioxane) for analysis. β,γ -Olefin R factor = 2.4071

Entry	[β,γ -olefin]	[Standard]	Area $_{\beta,\gamma\text{-olefin}}$	Area $_{\text{Standard}}$	$\frac{\text{Area}_{\beta,\gamma-o}}{\text{Area}_{\text{Standard}}}$	$\frac{\text{Conc}_{\beta,\gamma-o}}{\text{Conc}_{\text{Standard}}}$
1	0.0126	0.284	286.5	14248.7	0.020107097	0.044366197
2	0.0126	0.284	280.8	14461.6	0.019416939	0.044366197
3	0.0252	0.284	505.5	15091.6	0.033495454	0.088732394
4	0.0252	0.284	521.7	15254	0.034200865	0.088732394
5	0.0378	0.284	773.3	14685.8	0.052656307	0.133098592
6	0.0378	0.284	746.8	13939.4	0.053574759	0.133098592
7	0.0504	0.284	1086.7	14463.2	0.075135516	0.177464789
8	0.0504	0.284	1105.6	14304	0.077293065	0.177464789

Relative response factor (RRF) plot for β,γ -olefin



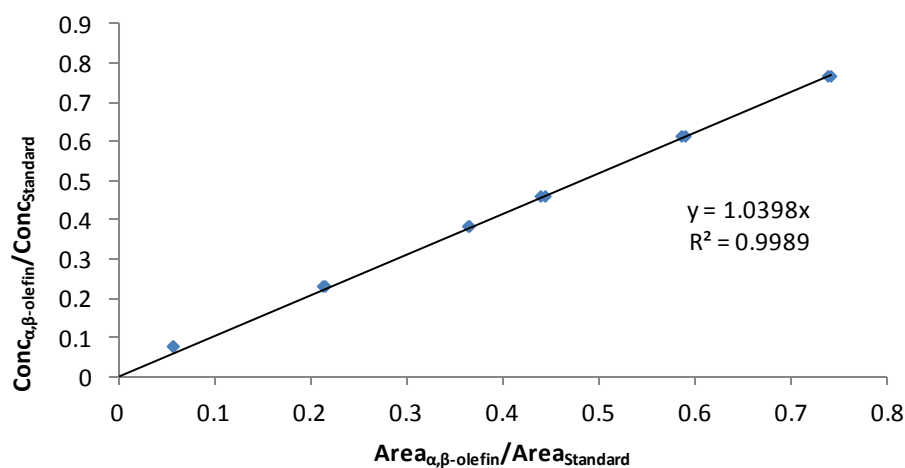
Relative response factor (RRF) for 6-phenyl-hex-3-en-2-one (3.36)



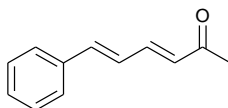
6-Phenyl-hex-3-en-2-one (0.100 g, 0.5739 mmol) was dissolved in dioxane (3.5 ml). 0.1 mL, 0.3 mL, 0.5 mL, 0.6 mL, 0.8 mL and 1 mL aliquots were taken, known volumes of the standard stock solution added and each diluted to 1 mL (dioxane) for analysis. α,β -olefin R factor = 1.0398

Entry	[α,β -olefin]	[Standard]	Area $_{\alpha,\beta\text{-olefin}}$	Area $_{\text{Standard}}$	$\frac{\text{Area}_{\alpha,\beta\text{-o}}}{\text{Area}_{\text{Standard}}}$	$\frac{\text{Conc}_{\alpha,\beta\text{-o}}}{\text{Conc}_{\text{Standard}}}$
1	0.0163	0.213	796.6	13870.7	0.05743041	0.076525822
2	0.0163	0.213	799.6	13772.9	0.05805604	0.076525822
3	0.0489	0.213	2386.9	11174.1	0.21361005	0.229577465
4	0.0489	0.213	2198.6	10185.2	0.21586223	0.229577465
5	0.0815	0.213	3774.2	10352.4	0.36457247	0.382629108
6	0.0815	0.213	3761	10278.2	0.36592010	0.382629108
7	0.0978	0.213	4679.9	10636.7	0.43997668	0.45915493
8	0.0978	0.213	4551.9	10237.3	0.44463872	0.45915493
9	0.1304	0.213	6130.1	10384.4	0.59031817	0.612206573
10	0.1304	0.213	5143.8	8771.2	0.58644199	0.612206573
11	0.163	0.213	6870.8	9263.9	0.74167467	0.765258216
12	0.163	0.213	8013.2	10847.9	0.73868675	0.765258216

Relative response factor (RRF) plot for α,β -olefin product



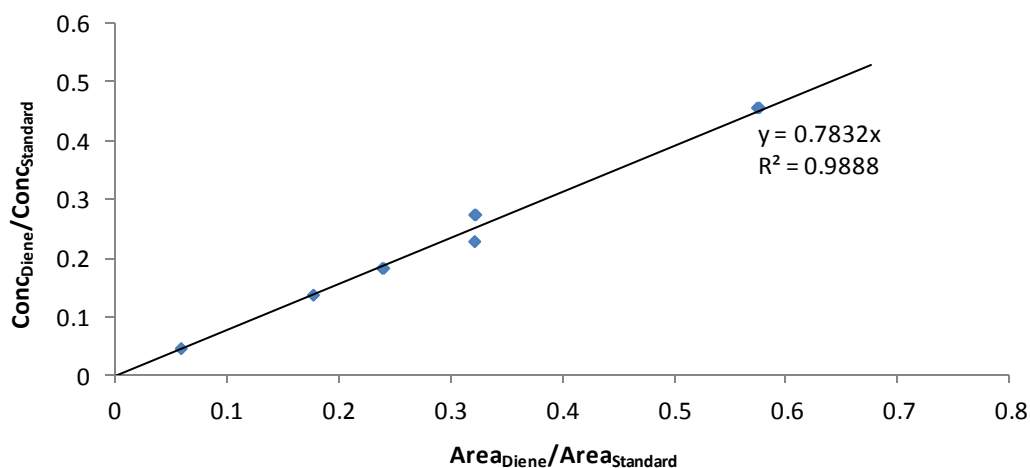
Relative response factor (RRF) for 6-phenyl-hexa-3,5-dien-2-one (3.37)



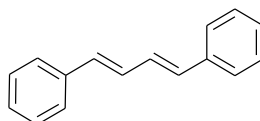
6-Phenyl-hex-3,5-dien-2-one (0.100 g, 0.5807 mmol) was dissolved in dioxane (3.0 ml). 0.1 mL, 0.3 mL, 0.4 mL, 0.5 mL, 0.6 mL and 1 mL aliquots were taken, known volumes of the standard stock solution added and each diluted to 1 mL (dioxane) for analysis. Diene addition product R factor = 0.7832

Entry	[Diene]	[Standard]	Area _{Diene}	Area _{Standard}	$\frac{Area_{Diene}}{Area_{Standard}}$	$\frac{Conc_{Diene}}{Conc_{Standard}}$
1	0.0194	0.426	1004.3	16905.5	0.059406702	0.045539906
2	0.0194	0.426	970.1	16311.3	0.059474107	0.045539906
3	0.0582	0.426	2921.1	16457.5	0.177493544	0.136619718
4	0.0582	0.426	2918.4	16429.5	0.177631699	0.136619718
5	0.0776	0.426	3878.2	16125	0.240508527	0.182159624
6	0.0776	0.426	3999.5	16728.5	0.239083002	0.182159624
7	0.097	0.426	5172.7	16072.9	0.321827424	0.227699531
8	0.097	0.426	5050.4	15708.7	0.321503371	0.227699531
9	0.1164	0.426	5922.3	18421	0.321497204	0.273239437
10	0.1164	0.426	5856.4	18145.2	0.322752023	0.273239437
11	0.194	0.426	10089.6	17573.6	0.574133928	0.455399061
12	0.194	0.426	10174.9	17664.9	0.575995335	0.455399061

Relative response factor (RRF) plot for diene addition product



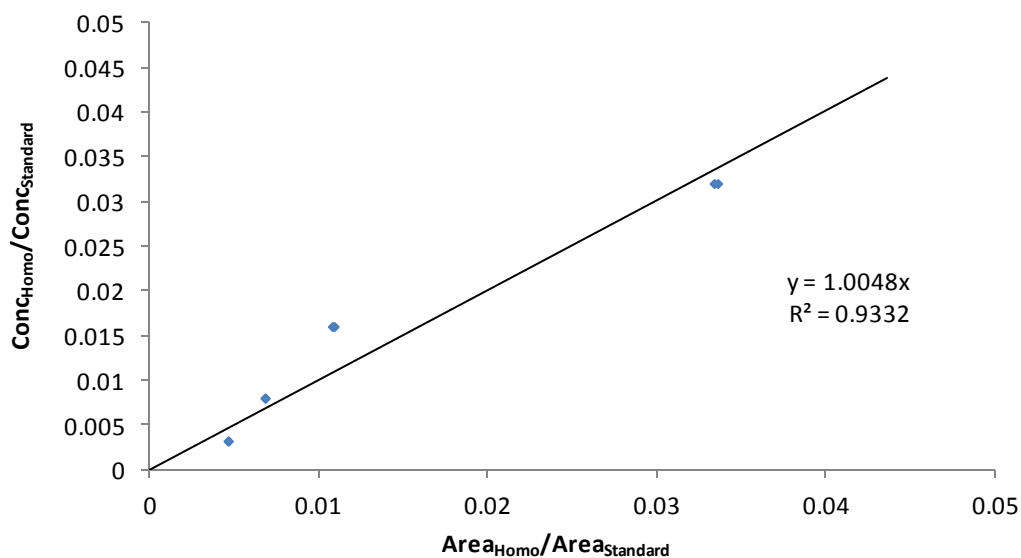
Relative response factor (RRF) for (*E,E*)-1,4-diphenyl-1,3-butadiene (3.38)



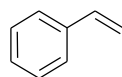
Homocoupled product, (*E,E*)-1,4-diphenyl-1,3-butadiene (0.0014 g, 0.00680 mmol) was dissolved in dioxane (0.3 ml). 0.01 mL, 0.025 mL, 0.05 mL and 0.1 mL aliquots were taken, known volumes of the standard stock solution added and each diluted to 1 mL (dioxane) for analysis. Homocoupled R factor = 1.0048

Entry	[Homocoupled]	[Standard]	Area _{Homo}	Area _{Standard}	$\frac{Area_{Homo}}{Area_{Standard}}$	$\frac{Conc_{Homo}}{Conc_{Standard}}$
1	0.000224	0.07	12.4	2666.1	0.004651	0.0032
2	0.000224	0.07	12.4	2649	0.004681	0.0032
3	0.00056	0.07	18.1	2648.2	0.006835	0.008
4	0.00056	0.07	18.1	2636.2	0.006866	0.008
5	0.00112	0.07	27.8	2542.1	0.010936	0.016
6	0.00112	0.07	28.2	2605.8	0.010822	0.016
7	0.00224	0.07	90.1	2680.6	0.033612	0.032
8	0.00224	0.07	90.1	2697.9	0.033396	0.032

Relative response factor (RRF) plot for homocoupled product



Relative response factor (RRF) styrene (3.39)



Protodeboronated product styrene (0.05 mL, 4.36 mmol) was dissolved in dioxane (4 ml). 0.05 mL, 0.1 mL, 0.4 mL, 0.6 mL, 0.6 mL and 0.8 mL aliquots were taken, 0.3 mL of the standard stock solution added and each diluted to 1.1 mL (dioxane) for analysis. Homocoupled R factor = 1.2439

Entry	[Styrene]	[Standard]	Area _{Styrene}	Area _{Standard}	$\frac{Area_{Styrene}}{Area_{Standard}}$	$\frac{Conc_{Styrene}}{Conc_{Standard}}$
1	0.049545455	0.387272727	1566.5	14970.1	0.10464192	0.127934272
2	0.049545455	0.387272727	1550.8	14934.8	0.103838016	0.127934272
3	0.099090909	0.387272727	3113.8	14680	0.212111717	0.255868545
4	0.099090909	0.387272727	3173.5	14942.2	0.212385057	0.255868545
7	0.396363636	0.387272727	13763.5	15214.4	0.904636397	1.023474178
8	0.396363636	0.387272727	13526	15035.8	0.899586321	1.023474178
9	0.594545455	0.387272727	18749.1	15317.1	1.224063302	1.535211268
10	0.594545455	0.387272727	18458	15214.2	1.213208713	1.535211268
11	0.792727273	0.387272727	25385.1	15789.1	1.60776105	2.046948357
12	0.792727273	0.387272727	25750	15930.6	1.616386075	2.046948357

Relative response factor (RRF) plot for protodeboronated product

